University of Alberta

Sensory Control of Human Infant Stepping

by

Marco Yiu Chung Pang ©

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Doctor of Philosophy

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ABSTRACT

Evidence from animal studies has shown that the spinal cord alone is able to produce alternating flexor and extensor activity for walking. However, the motor output is highly modifiable by sensory input. This allows the adaptation of the walking pattern to the external environment encountered in natural walking situations. In human infants, the stepping response is thought to be primarily controlled by the brainstem and spinal cord circuitry. Studying the effects of different sensory inputs on the stepping response in human infants will shed light on how the subcortical locomotor circuitry controls walking in humans. This thesis consists of four projects on sensory control of human infant stepping. First, it was found that hip extension and load reduction combine to determine the timing of the stance to swing transition in forward stepping, showing sensory input from the limb could powerfully change the structure of the step cycle. Second, unilateral disturbances that initiate or prolong the swing phase on one side produce compensatory response on the other side, so that equilibrium is preserved. It indicates that the movements of the two legs are well coordinated despite perturbations, well before the onset of independent walking. Third, the most powerful hip motion to trigger the swing phase is a function of the direction of walking, which indicates the presence of selective gating of sensory input from the hip as the direction of walking changes. Finally, it was shown that some infants show high stepping immediately after the withdrawal of repetitive trip-inducing stimuli, indicating the presence of adaptive locomotor plasticity in response to exposure to sustained perturbations during walking. Together, this thesis shows that the stepping response in human infants can be greatly influenced by different types of sensory input. This thesis also highlights the striking similarities between the behavior of the subcortical locomotor circuitry for stepping in human infants and that in cats.

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CHAPTER 1 - GENERAL INTRODUCTION

1.1 Introduction

The ability to locomote, whether it be swimming, flying or walking, is of paramount importance for the survival of the animals. Behaviors such as searching for food, escaping from predators all require the ability to locomote effectively. In order for animals to locomote successfully in a changing environmental context, not only must they be able to generate the rhythmic locomotor movements, but they must also be able to maintain equilibrium and adjust the basic rhythmic pattern to various environmental constraints such as changes in terrain and presence of obstacles. The sensory inputs from the periphery inform the locomotor circuitry of such changes and play an important role in shaping the motor output appropriate for the behavioral state of the animal. Sensory feedback is thus essential in achieving adaptive locomotion.

Sensory control of locomotion has been extensively studied in lower animals. Whether sensory feedback influences the human locomotor circuitry in similar ways is the major purpose of this thesis. The objectives of this thesis are to examine 3 specific issues related to sensory control of locomotion in humans: (1) how different types of sensory input influence the stance to swing phase transition in different forms of walking, (2) how the movements of the two limbs are coordinated to preserve equilibrium in response to transient perturbations during walking, and (3) how the locomotor pattern adapts to sustained perturbations. This thesis aims to shed more light on how the sensory inputs to the locomotor circuitry in humans are organized. While many regions in the nervous system are responsible for controlling different aspects of locomotion, the following discussion will be limited to the issues relevant to the experimental findings in this thesis.

1.2 Evidence for a Central Pattern Generator for Locomotion

Since the late 19th and early 20th century, it has been recognized that reduced animals are able to demonstrate coordinated locomotor movements, particularly in spinalized or decerebrate cats and dogs (Brown, 1911; Freusberg, 1874; Philippson, 1905; Sherrington, 1910a, b). It was initially thought that the alternating flexion and extension movements during locomotion are produced by a chain of peripheral reflexes (Sherrington, 1910a,b). According to this hypothesis, the sensory signals produced by the first movement initiate a second movement. The afferent signals associated with the second movement would in turn produce another reflexive movement and so on. However, later experimental evidence showed that peripheral sensory feedback is not necessary to produce the rhythmic limb movements. Graham Brown (1911) demonstrated that following a low thoracic transection in the cat, the deafferented lumbosacral spinal cord is still able to generate rhythmical activity in the ankle flexor and extensor muscles, without any input from the descending tracts or sensory information from either hindlimb. He concluded that the controlling centers for generating the rhythmic movements must reside in the spinal cord (Brown, 1911, 1914). He proposed the famous half-centre model for the control of stepping movements. In this model, the spinal cord contains a flexor half-centre that controls the flexor muscles and an extensor half-centre that controls the extensor muscles. The mutual inhibitory connections between the two centers account for the generation of the alternating flexion and extension movements (Brown, 1911, 1914). In this model, it is not specified whether the half-centers are actually motoneurons or interneurons. Nevertheless, according to Brown (1911), sensory input only plays a 'regulative' role, not a 'causative' role in neural control of locomotion.

More than half a century later, using acute spinal cats treated with L-Dihydroxyphenylalanine (L-DOPA), Jankowska et al. (1967a) discovered that electrical stimulation of small-diameter joint, cutaneous or muscle afferents (flexor reflex afferents or FRA) produced long-latency and long-lasting excitation of ipsilateral flexor motoneurons and inhibition of ipsilateral extensor motoneurons. Stimulation of the contralateral FRA, however, produced exactly opposite effects (excitation of ipsilateral extensors and inhibition of ipsilateral flexors). In addition, sequences of alternating flexor and extensor activity similar to that observed in locomotion were sometimes obtained by FRA stimulation, particularly when L-DOPA was administered after treatment with nialamide

(Jankowska et al. 1967a,b). Moreover, applying a conditioning stimulus to the contralateral FRA produced an effective inhibition of the excitatory postsynaptic potential (EPSP) in ipsilateral flexor motoneurons evoked by stimulating ipsilateral FRA. These experimental findings suggest the presence of mutual inhibitory mechanisms between excitatory interneuronal pathways to flexor and extensor motoneurons that account for the alternating flexor and extensor activity on the same side and also between the left and right side. It was proposed that the neurons that produce these rhythmic bursts might be part of the locomotor network itself, although it is also possible that these interneurons are not part of locomotor network but interneurons intercalated between the locomotor network and the motoneurons (Edgerton et al. 1976). The findings by Jankowska et al. (1967a,b) also lend support to the half-centre model originally proposed by Graham Brown (1911), in which the mutually inhibitory flexor and extensor half-centers are the key feature of the pattern-generating network.

The half-centre model has its own limitations. While it can account for the alternation between flexor and extensor activity, it does not explain the complex muscle activity seen in real locomotion. The muscle activity involved in locomotion is more sophisticated than a simple alternation between flexors and extensors. In particular, the timing of activation of flexor and bifunctional muscles is quite individualized. In cat locomotion, for example, the activity of hip flexor iliopsoas (IP) is maintained almost throughout the whole swing phase, whereas semitendinosis (St) shows an early burst which rapidly declines and a later burst in the extensor phase (Engberg and Lundberg, 1969). Is the spinal cord capable of generating such complex muscle activity? Grillner and Zangger (1975, 1979, 1984) found that after deafferentation of the hindlimbs in the mesencephalic cat, the muscle activation pattern during walking remained very similar to that in the intact cat. The subtle temporal features of activation of different muscle groups were retained in the deafferented preparation (e.g. short burst of St in the extensor phase). Later, Pearson and Rossignol (1991) found that in early-chronic spinal cats (within one week after spinalization), the fictive locomotor pattern was characterized by more or less synchronous activity of flexors alternating with extensor activity. Double burst activity in St and anterior sartorius was not observed. However, in late-chronic spinal cats, the fictive locomotor pattern became more complex and double burst activity of the aforementioned flexors was often observed (Pearson and Rossignol, 1991). Plastic changes in the spinal cord after spinalization may account for the difference between early and late chronic spinal cats. Nevertheless, their results show that the spinal cord is capable of generating complex activity without phasic sensory feedback. The half-centre model proposed by Brown (1911) is thus insufficient to explain the intricate muscle activity generated during locomotion.

In light of the above limitations, other alternative models of the locomotor pattern generator have been proposed. Perret and Cabelguen (1980) found that bifunctional muscles showed complex activities and alpha motoneurons of these muscles receive both flexor and extensor commands. They suggested that the temporal ordering of the activity of these muscles depends upon the relative grading of the strength of the commands from the flexor and extensor centers. For example, posterior biceps-semitendinosis motoneurons receive excitation during both flexor and extensor phases. It was suggested that the primary excitatory input comes directly from the extensor centre. The excitatory influence during the flexor phase arrives indirectly through interneurons (Orsal et al. 1986).

Grillner (1981) proposed an alternative model in an attempt to explain how the spinal cord generates the complex muscle activity during locomotion. In his model, Grillner (1981) defined the group of spinal neurons producing the locomotor movements as the spinal central pattern generator (CPG). The CPG consists of a mosaic of subunits called unit burst generators that control individual muscle groups around a joint (i.e. hip flexors). Each unit burst generator is capable of producing its bursting output and the interconnections and coupling between these subunits determine the relative phase of the muscles in locomotion (Grillner, 1981). Findings in various species, including the tadpole (Roberts et al. 1997), lamprey (Matsushima and Grillner, 1992) and mudpuppy (Cheng et al. 1998) seemed to support such an organization model. In the tadpole and lamprey, each spinal cord segment contains a left and a right half-centre which control the muscular contractions in a coordinated manner to produce swimming, supporting the idea of smaller unit pattern generators. Moreover, the phase coupling between consecutive segments can be changed by altering the local excitability of different segments of the spinal cord, resulting in different directions of swimming. These results thus support the idea that the coupling of the unit pattern generators can be changed to produce different motor behaviors (Matsushima and Grillner, 1992; Tunstall and Roberts, 1991). In the mudpuppy, electrical stimulation of part of the 2nd cervical (C2) segment of the spinal cord produces rhythmic elbow flexor bursts whereas stimulation of part of segment C3 produces rhythmic elbow extensor bursts. Moreover, stimulation of segment C3 rostral to the dorsal root induces rhythmic wrist flexion and extension (Cheng et al. 1998). These data show that there are separate centers in the spinal cord for generating rhythmic activity in the flexors and extensors. In addition, there appears to be separate centers for producing rhythmic activity in muscles around different joints, agreeing well with the concept of unit burst generators proposed by Grillner (1981). Thus, locomotion is not controlled by the simple alternating activity of a flexor half-center and an extensor half-center as proposed by Brown (1911, 1914). This is not surprising, because successful locomotion requires precise coordination of movements at multiple joints in the limbs, much more complicated than a simple alternation between synchronous flexion (swing phase) and extension movements (stance phase). The half-center model proposed by Brown is indeed an over-simplified model of the locomotor CPG.

The model proposed by Grillner (1981) supports the idea that portions of the CPG may be involved in generating other motor behaviors. Moreover, such a model has the advantage of allowing modifications of the output by simply altering the coupling between the unit burst generators (e.g. forward and backward walking). In fact, distinct phase shifts in the timing of activity of different muscles in forward and backward walking were observed in lobsters and humans (Ayers and Davis, 1977; Thorstensson, 1986). However, the actual organization of the CPG must be more complex than simply altering the coupling between the unit burst generators between different joints. For example, in cats, the same motor synergy is used for both forward and backward walking. The muscles active in the stance phase for backward walking do not become active in the swing phase during forward walking (Buford and Smith, 1990; reviewed in Pearson, 1993). Therefore, while the model proposed by Grillner (1981) succeeds in explaining the ability of the pattern generator to produce complex muscle activity and different variations of the same behavior, the organization of the locomotor pattern generating network must be more complicated than that proposed by his model (reviewed in Pearson, 1993). Nevertheless, both Brown's and Grillner's models remain useful conceptual models in understanding the neural control of locomotion.

While there is clearly a spinal CPG for locomotion in the lower mammals, is there a similar generator in primates? Philippson (1905) first reported that spinalized monkeys showed alternating movements of the hindlimbs approximately one month after spinal transection. On the other hand, Eidelberg and colleagues (1981) were unable to obtain fictive locomotion in acute spinalized macaque monkeys treated with L-DOPA / nialamide. They also failed to induce stepping movements by treadmill stimulation in chronic spinalized macaque monkeys, despite the application of clonidine or skin stimulation (Eidelberg et al. 1981). More recently, rhythmic activity was obtained in flexor and extensor nerves in the hindlimbs in some spinalized and paralyzed marmoset monkeys after application of excitatory amino acids or clonidine (Fedirchuk et al. 1998). In general, it is more difficult to induce alternating activity in these monkeys than in cats. The fictive locomotor pattern is incomplete (e.g. alternation of flexors and extensors in one limb without alternation in the other). In addition, pharmacological agents effective in initiating the rhythm in other species, such as L-DOPA, noradrenaline and serotonin, are ineffective in inducing rhythmic activity in the primate spinal cord (Fedirchuk et al. 1998). Taken together, the evidence for a locomotor CPG is less conclusive in the primates. The relative difficulty of eliciting locomotor activity in the primates seems to indicate that the activation of the locomotor pattern generator depends more on supraspinal input in primates than in lower mammals.

The next question is: is there a locomotor CPG in the human spinal cord? The evidence we have so far is indirect. The first line of evidence comes from reports of rhythmic movements and muscle contractions in spinal cord injured subjects. In the early 20th century, several cases of alternating stepping-like activity in patients with incomplete spinal cord lesions due to gunshot injuries were reported (Holmes, 1915). Kuhn (1950) claimed that spontaneous rhythmic stepping like movements were sometimes observed in a group of patients with chronic spinal cord injury. However, no other details were given. Myoclonic activity [0.3 - 0.6 Hertz (Hz)] in the extensor muscles of the trunk and lower limbs in a patient with clinically complete cervical spinal cord injury was reported by Bussel (1988). Calancie (1994) also reported involuntary stepping-like movements (0.3 Hz) in a patient with incomplete cervical spinal cord injury, when lying supine with the hips extended. In patients with complete spinal cord injury, locomotor electromyography (EMG) activity could be obtained while these patients performed assisted stepping movements on the treadmill (Dietz et al. 1995).

Other evidence supporting the existence of a CPG for locomotion in humans comes from several studies on the spinal reflex responses of spinal cord injured subjects. In patients with clinically complete spinal cord injury, electrical stimulation of the FRA evokes similar reflex responses as in cats (Roby-Brami and Bussel, 1987, 1990, 1992). For example, late flexor discharges on one side concur with inhibition of contralateral late flexor discharges (Roby-Brami and Bussel, 1992). The similar responses between humans and cats to stimulation of FRA suggest that the spinal reflex circuitry in humans may bear resemblance to the L-DOPA networks in cats, which are believed to be part of the locomotor pattern generator by some researchers (Jankowska et al. 1967 a, b; Lundberg, 1980).

The pattern-generating capacity of the human spinal cord has also been demonstrated in other experimental conditions. By applying tonic vibration (20-60 Hz) to one of the leg muscles in healthy subjects, cyclical movements with alternating activity of flexor and extensor muscles in the leg are observed (Gurfinkel et al. 1998). The coordination of movements between different joints is very similar to that in voluntary stepping. Occasionally, stepping movements of both legs can also be induced. It was suggested that the tonic inflow of sensory input due to vibration initiates and maintains the CPG activity (Gurfinkel et al. 1998). Dimitrijevic et al. (1998) were also able to elicit stepping-like motions in patients with complete thoracic spinal cord injury by using tonic epidural electrical stimulation (25-60Hz) to the spinal cord at L2 level by means of implanted electrodes.

Overall, whether a locomotor CPG exists in humans remains controversial. The involuntary stepping-like movements reported by

Calancie (1994) are observed in a patient with incomplete spinal cord injury. Thus, the involvement of descending input in producing these movements cannot be ruled out. Although locomotor EMG or stepping movements could be obtained through treadmill training or electrical stimulation of the spinal cord in patients with complete spinal cord injury (Dietz et al. 1995; Dimitrijevic et al. 1998), the sensory input is intact. Thus, the effects of movement-related feedback cannot be ruled out. Nevertheless, considering the evidence we have so far in humans, and the compelling evidence of existence of a locomotor CPG in many other animal species (reviewed in Orlovsky et al. 1999), it is very likely that a locomotor CPG exists in humans, just as in other species.

1.3 Flexibility of pattern generating networks

The organizational model of the CPG proposed by Grillner (1981) suggests that the coupling between the different unit burst generators can be altered, thereby allowing the production of various motor behaviors. On the other hand, based on the results from spinal microstimulation or intraspinal NMDA iontophoresis in frogs and rats, it was proposed that the premotor circuits of the spinal cord are organized into discrete modules, each of which controls the activity of muscles in subgroups (also called synergies). It was suggested that these modules could be used by the circuitry underlying generation of rhythmic patterns. The activation of different combinations of modules produces a large repertoire of motor behaviors (Saltiel et al. 1998, 2001; Tresch and Bizzi, 1999; Tresch et al. 1999). Although this concept of modular organization of the spinal cord is different from the model proposed by Grillner (1981), both concepts are similar in that both discrete modules and unit pattern generators can be viewed as neural elements grouped together that control the activation of small groups of muscles. Activity of different modules or unit burst generators could be combined in many different ways to produce various motor behaviors. Ample evidence has shown that many pattern-generating neuronal circuits are multifunctional. The reconfiguration of neural networks to produce different motor patterns could be accomplished by changes in peripheral sensory input, neuromodulatory substances or signals from other regions of the central nervous system (reviewed in Marder and Calabrese, 1996; Pearson, 1993).

The idea of multifunctional neural networks and shared neural circuitry can be well illustrated in the stomatogastric system in crustacea. In this system, there are four interconnected pattern generating networks that control the esophageal, cardiac sac, gastric and pyloric rhythms, respectively. When the pyloric suppressor (PS) neuron is active, the same neurons are coordinated to create a single rhythm, thereby producing a swallowing like behavior (Meyrand et al. 1991). In another example, the coordination of tooth movements in the gastric mill system in the lobster can be tremendously influenced by a neuromodulatory substance called proctolin. At low concentrations, the squeezing pattern is evoked. At higher concentrations, the same circuit produces a cut-and grind mode (Heinzel, 1988; Heinzel and Selverston, 1988). Apart from the stomatogastric system in the crustacea, the presence of multifunctional circuits is also found in many other invertebrate species. The same neural circuit is modified to produce withdrawal and swimming in *Tritonia* (Getting and Dekin, 1985), gill withdrawal and respiratory pumping in *Aplysia* (Wu et al. 1994), jumping and kicking in the locust (Gynther and Pearson, 1989).

The idea of shared neuronal circuitry for different behaviors is also supported by evidence in vertebrates. Neurons in the same circuit are involved in swimming and struggling in *Xenopus* embryos (Soffe, 1993). Using *in vitro* brainstem slice preparation from mice, Lieske et al. (2000) showed that many neurons in the ventral respiratory group are active during different respiratory patterns, such as regular breathing, sighing and gasping. The scratch reflex in the turtle also provides indirect evidence of a shared circuitry for various motor patterns. Three forms of scratch reflex exist in the turtle, including rostral, pocket and caudal scratch (Mortin et al. 1985). Each form of the scratch reflex can be elicited by stimulating a specific area of the skin. Interestingly, blended responses can be evoked by stimulating the transitional zones that are located between the receptive fields of the different forms of the reflex. Moreover, it has been shown that the three forms of the scratch reflex are mediated by spinal cord segments located within the same region, suggesting shared neural elements among the various forms of the scratch reflex (Mortin and Stein, 1989). Analysis of the hindlimb movements during scratching and swimming also reveals striking similarities between different behaviors such as rostral scratch and forward swimming, suggesting that there may be shared spinal circuitry for the two behaviors (Field and Stein, 1997).

Experimental evidence also showed that the same pattern-generating network could produce different forms of locomotor behavior. In the lamprey, when the N-Methyl-D-Aspartate (NMDA) concentration is higher in the rostral segments than the caudal segments, the fictive swimming pattern resembles forward swimming. The motor pattern is switched to backward swimming if the NMDA concentration becomes higher in the caudal segment than the rostral segments (Matsushima and Grillner, 1992). In spinalized dogfish, applying a brief tactile stimuli to the rostro-ventral surface of the body changes the swimming pattern from forward to backward (Grillner, 1974). Indirect evidence also suggests that the same CPG generates different forms or directions of walking in cats, such as backward walking, crouched walking and slope walking (Buford and Smith, 1990; Smith et al. 1993, 1998; Trank et al. 1996; Carlson-Kuhta et al. 1998).

In adult humans, there is smooth transition between walking and running (Grillner et al. 1979; Thorstensson and Roberthson, 1987) and between different directions of walking (Stein et al. 1986). By comparing the kinematics and muscle activation patterns, some studies suggested that the same generator produces different directions of walking (Grasso et al. 1998; Thorstensson, 1986; Winter et al. 1989). Lamb and Yang (2000) found that human infants also showed smooth transition between different directions of walking. Most of the infants who show forward stepping also express stepping in other directions. Moreover, in backward and sideways stepping, the changes in stance and swing phase duration with different speeds are very similar to those in forward walking. These authors suggested that the different directions of walking are controlled by the same locomotor circuitry. More recently, Earhart et al. (2001) demonstrated that after walking on the perimeter of a rotating disk, the curved locomotor trajectories of forward and backward walking over stationary ground were very similar. The transfer of this podokinetic learning from forward to backward walking supports the idea of a similar circuitry controlling both forward and backward walking. Such a transfer of learning also occurs between stepping and hopping (Earhart et al. 2002a). Thus, it is likely that the same locomotor circuitry is capable of producing different forms of walking in humans, just as in lower animals.

1.4 The role of brainstem in walking

The locomotor CPG in the spinal cord is subject to the control of the brainstem pathways. Various regions in the brainstem are involved in the initiation of locomotion, regulation of postural activity and modifications of muscle activity in the legs during adaptive locomotion. Electrical stimulation of many brainstem regions in the cat can produce locomotion (reviewed in Armstrong, 1986; Whelan, 1996). It has long been known that stimulation of the mesencephalic locomotor region (MLR) produces locomotion in decerebrate and intact cats (Shik et al. 1966; Sirota and Shik, 1973). As the intensity of the stimulation was increased, the propulsive force developed in the hindlimbs was also increased, while the speed of the treadmill belt was kept constant (Shik et al. 1966). At stronger intensity of stimulation while the speed of the treadmill remained the same, the gait pattern changed from an alternating pattern (i.e., walk or trot) to in-phase pattern (i.e., gallop). Thus, the evidence suggests that the activity of MLR has a powerful impact on the intensity of muscle contraction in the legs and also the speed and mode of progression (Orlovsky et al. 1999). The MLR is not the only region in the brainstem that can produce locomotion because destruction of this region does not prevent the otherwise intact cat from walking (Shik and Orlovsky, 1976; Sirota and Shik, 1973). Other regions of the brainstem such as the subthalamic locomotor region, pontomedullary locomotor region and medial reticular formation can also produce locomotion (reviewed in Armstrong, 1986; Whelan, 1996).

Several pathways from the brainstem may be involved in the initiation of locomotion by activating the spinal locomotor CPG (Mori et al. 1992). The locomotor activity produced by stimulation of MLR was not abolished by caudal brainstem lesion that isolated the lateral tegmentum or by dorsal hemisections of the C2-3 spinal cord, indicating that the descending pathway from the MLR projects through the medial reticular formation and ventral part of the spinal cord (Noga et al. 1991). On the other hand, locomotion produced by stimulation of pontomedullary locomotor region (located in the lateral tegmentum of the brainstem) was abolished by reversible cooling of either the medial reticular formation or the ventrolateral funiculus of the spinal cord. Therefore, locomotion can also be initiated through a second pathway originating from the pontomedullary locomotor region to the medial reticular formation that projects through the ventral half of the spinal cord (Noga et al. 1991). However, the pontomedullary locomotor region could also produce locomotion following surgical isolation of the lateral tegmentum of the brainstem from the medial reticular formation and the MLR. Lesion of the dorsal part of the spinal cord also resulted in loss of pontomedullary locomotor region evoked locomotion in some cases. Thus, a third pathway from the pontomedullary locomotor region projecting caudally through the dorsal part of the spinal cord cannot be ruled out (Noga et al. 1991).

Normal locomotion also requires an adequate level of extensor tone in the legs for weight support. Stimulation of an area within the dorsal tegmental field reduced the extensor tone, whereas stimulation of ventral tegmental field increased the extensor tone (Mori, 1987; Mori et al. 1992). The stimulation of these tegmental regions could interact with the signals from MLR to produce changes in the vigor of locomotion. For example, in decerebrate cats, simultaneous stimulation of MLR and ventral tegmental field changed the alternating walking pattern to a galloping pattern (Mori et al. 1978).

Other pathways in the brainstem such as the vestibulospinal or reticulospinal tract also play a significant role in regulating the postural activity during locomotion. During quadrupedal locomotion on a level treadmill surface, many vestibulospinal neurons in the intact cat showed high tonic discharge level that was phasically modulated with the locomotor rhythm. Some cells showed a peak activity time-locked to the activity of the extensors of the ipsilateral hindlimb while other neurons showed a peak activity that was time-locked to the activity of either extensor or flexor muscles of a single limb (Matsuyama and Drew, 2000a). During uphill walking, the vestibulospinal neurons also increased the peak discharge frequency (Matsuyama and Drew, 2000b). It was suggested that the vestibulospinal neurons regulate the overall level of EMG activity in the limbs to suit the needs for increased or decreased muscle tonus for weight support (Matsuyama and Drew, 2000a, b). The discharge activities of some reticulospinal neurons are also phasically modulated with the locomotor rhythm (Matsuyama and Drew, 2000a, b). Most of the locomotor related reticulospinal neurons showed one or two peaks of activity that were time-locked to either flexor or extensor muscles (Matsuyama and Drew, 2000a). When the treadmill surface was tilted to the left or right side, the neurons that discharged twice in each step cycle during normal stepping was modulated in that one burst of activity increased during left tilt and the other during right tilt (Matsuyama and Drew, 2000b). During the locomotor task in which the intact cat was required to step over an obstacle, many reticulospinal neurons increased their discharge when either the ipsilateral or the contralateral limb was the leading limb to pass over the obstacle (Prentice and Drew, 2001). It was suggested that the reticulospinal neurons are involved in signaling the timing and magnitude of the postural activity during adaptive locomotion, especially when the gait pattern is asymmetric (Matsuyama and Drew, 2000a, b; Prentice and Drew, 2001). These findings are consistent with the results from lesion studies. Destruction of the lateral vestibular nucleus caused a significant loss of extensor muscle tone in the decerebrate cat (Bach and Magoun, 1947; Fulton et al. 1930). Extensive lesions in the ventral and ventrolateral funiculi of the spinal cord, which caused damage to the vestibulospinal and reticulospinal pathways, resulted in poor weight support and severe postural deficits (Brustein and Rossignol, 1998).

The rubrospinal tract is also involved in adaptive locomotion. During unperturbed locomotion in the decerebrate and intact cat, most of the rubrospinal tract neurons showed a peak activity during the swing phase (Lavoie and Drew, 2002; Orlovsky, 1972). Almost all recorded rubrospinal neurons showed increased peak activity during the swing phase when the contralateral limb was the leading limb to step over the obstacle (Lavoie and Drew, 2002). The results indicate that the rubrospinal tract contributes to the gait modifications during adaptive locomotion. It plays a role in modifying the activity of muscles, primarily that of the flexors, to produce a change in the limb trajectory to overcome the obstacle (Lavoie and Drew, 2002).

In summary, while the CPG in the spinal cord can generate the basic locomotor pattern, various pathways originating from the brainstem can have powerful modulatory effects on the locomotor pattern. Multiple regions, including the MLR and the pontomedullary locomotor region are able to initiate locomotion (Noga et al. 1991; reviewed in Whelan, 1996). The intensity of the signal from MLR also determines the propulsive force produced in the hindlimb muscles as well as the mode of progression (alternating or in-phase) (Orlovsky et al. 1999). Reticulospinal and vestibulospinal tract contribute to changes in postural activity that accompanies gait modifications during perturbed locomotion (Matsuyama and Drew, 2000a, b; Prentice and Drew, 2001). The rubrospinal tract, on the other hand, contributes to the augmentation of flexor muscle activity that is required to overcome an obstacle during the swing phase of walking (Lavoie and Drew, 2002). The activity of different brainstem pathways allows the animal to maintain equilibrium during locomotion and to adapt the basic locomotor movements to the environmental constraints and to the behavioral goals of the animal (reviewed in Armstrong, 1986).

1.5 Sensory control of walking

1.5.1 Adjustment to changes in external environment

In order to locomote successfully in the changing environmental context, the stereotypical movements generated by the CPG must be adapted to the external conditions. Sensory inputs from the limbs inform the central locomotor networks of changes in the locomotor environment and enable the animal to compensate for such changes. Numerous studies reported that the locomotor rhythm after deafferentation is more labile (Giuliani and Smith, 1987; Grillner and Zangger, 1975, 1979, 1984; Wetzel et al. 1976). The deafferented hindlimb is often misplaced, thus making it impossible for the animal to cross a narrow runway for the first week after deafferentation (Goldberger, 1977). Using overdoses of pyridoxine to induce large fiber peripheral sensory neuropathy in cats, major impairment in walking is observed (Allum et al. 1998). There is severe ataxia, abnormal limb movements and impaired interlimb coordination. Many animals are not able to walk without harness support and the maximum speed attained is substantially reduced (no higher than 0.2m/s). Moreover, these animals are unable to adapt to changes in terrain or loading (Allum et al. 1998). Lajoie et al. (1996) also found that walking was extremely difficult for human subjects with large-fiber sensory loss, even on a flat surface. Hence, the stereotypical movements produced by the CPG are of little use in the absence of sensory input. Sensory feedback does more than just fine-tuning the basic locomotor rhythm (Prochazka and Yakovenko, 2001). Functional locomotion in the real world necessitates the presence of sensory input.

The locomotor pattern must also be adapted to the presence of obstacles. Many studies have investigated the corrective reactions in cat locomotion when a mechanical or electrical stimulus is applied to the dorsum of the paw simulating the presence of an obstacle (Drew and Rossignol, 1985, 1987; Duysens, 1977; Duysens and Loeb, 1980; Forssberg et al. 1975, 1977; Forssberg, 1979; Matsukawa et al. 1982; Miller et al. 1977; Prochazka et al. 1978; Wand et al. 1980). Significant changes in the structure of the step cycle and EMG responses are induced by such stimuli. If the stimulus is applied during the swing phase, flexor activity is promoted, resulting in a high step (Forssberg et al. 1975, 1977; Wand et al. 1980). This is often referred to as the stumbling corrective response. The increased flexion in the limb allows the foot to step over any obstacles encountered during swing phase and prevent a fall. When the same stimulus is applied during stance phase, no increase in flexor activity is observed. This is also functionally appropriate because flexor activity at this time of the step cycle would probably result in a fall as the contralateral limb is going through the swing phase. Similar findings have been reported in spinal (Forssberg et al. 1975, 1977), decerebrate (Duysens, 1977; Matsukawa et al. 1982; Miller et al. 1977), and intact cats (Drew and Rossignol, 1985, 1987; Duysens and Loeb, 1980; Forssberg, 1979; Prochazka et al. 1978; Wand et al. 1980).

Numerous human experiments using mechanical perturbations of the dorsum of the foot (Eng et al. 1994; Schillings et al. 1996, 2000) or electrical stimulation of the superficial peroneal nerve (nerve supply of the dorsum of the foot) (Van Wezel et al. 1997; Zehr et al. 1997) also yield similar results. Such well-organized response to the presence of an obstacle requires intact sensory input. When the dorsum of the foot is anaesthetized, the stumbling corrective response is abolished, suggesting that the integrity of the cutaneous reflex pathways from the dorsum of the foot is required (Drew and Rossignol, 1987; Forssberg et al. 1975, 1977). More recently, Bouyer and Rossignol (1998) also reported that following complete cutaneous neurectomy in otherwise intact cats, the ability to walk on a horizontal ladder or a narrow beam was lost for the first few weeks despite a nearly normal locomotor pattern while walking on the treadmill. Taken together, these experimental findings indicate that sensory input is essential in achieving functional locomotion in the real world.

1.5.2 Sensory control of stance to swing transition

Despite the central origin of spinal stepping, it has long been known that sensory input has a very important role in regulating locomotor movements (Sherrington, 1910a). The role of sensory input on the control of locomotion was not extensively investigated until in mid 70s and early

80s. One of the most studied area is the afferent control of the transition from stance to swing phase.

Similar to intact cats (Halbertsma, 1983) and mesencephalic cats (Kulagin and Shik, 1970), spinal cats are able to adjust to a large range of treadmill speeds (Forssberg et al. 1980a). With increased speed, the step cycle duration decreases as a power function. The reduction of the step cycle duration is mainly due to the shortening of the stance phase while the swing phase remains relatively constant (Forssberg et al. 1980a; Grillner, 1973). Thus, sensory signals generated during the stance phase must have a regulatory effect on the period of extensor activity, and hence the transition from stance to swing phase (Halbertsma, 1983).

Grillner and Rossignol (1978) first proposed that hip extension is an important factor in determining the timing of the transition from stance to swing phase. They found in walking chronic spinal cats that the alternating flexor and extensor activity of the limb was terminated and replaced by tonic activity of the extensors if the hip was prevented from attaining an extended position. When the hip was slowly extended to a critical position, a strong flexion movement was suddenly initiated. No such phenomenon occurred by manipulating the knee and ankle position while the hip joint was kept in flexion (Grillner and Rossignol, 1978). While these findings support the role of hip position in regulating the transition, the study did not address the specific types of afferents involved in mediating such responses.

Subsequent experiments indicate an important role of stretch-sensitive afferents of the hip in the control of the stance to swing transition during walking. Andersson and Grillner (1981, 1983) demonstrated in acute spinal cats that locomotor rhythm could be entrained by ramped or sinusoidal movements of the hip. In their preparations, the hindlimbs were extensively denervated, leaving only the hip joint capsule and a small number of muscles around the joint intact, implicating that hip joint afferents or hip muscle spindle afferents may be involved. Later, Kriellaars et al. (1994) found that entrainment of the fictive locomotor rhythm was still possible in decerebrate cats even if the hip joint was denervated. Moreover, the entraining effect became weaker with progressive reduction of sensory input from the muscles. However, this study did not examine the effect of denervating the hip muscle afferents and leaving the hip joint and /or skin afferents about the hip intact. Therefore, the possibility that hip joint afferents may contribute to the stance to swing phase transition in real locomotion cannot be ruled out. Nevertheless, the study did show that the muscle spindle afferents from the hip could exert powerful influence on the locomotor rhythm (Kriellaars et al. 1994).

Hiebert et al. (1996) later provided evidence that group I stretch-sensitive afferents from the hindlimb flexor muscles influenced the timing of the stance to swing transition. In walking decerebrate cats, application of ramp stretches to iliopsoas (IP), tibialis anterior (TA) or extensor digitorium longus (EDL) individually during stance phase shortened the duration of extensor activity and promoted the initiation of the swing phase. Activation of Ia afferents in IP or EDL muscles through vibration or electrical stimulation during stance phase also produced similar effects (Hiebert et al. 1996).

Stretch-sensitive group II afferents from flexors have also been indicated for controlling the timing of the stance to swing transition. In walking decerebrate cats, stimulation of the TA nerve at group II strength resets the locomotor rhythm to flexion (Hiebert et al. 1996). In paralyzed high spinal cats, stimulation of posterior biceps-semitendinosis and deep peroneal nerves at group II strength terminates the extensor burst and promoted the initiation of flexor burst (Schomburg et al. 1998). Again, some differences between preparations are noted. In paralyzed decerebrate cats, stimulation of TA and posterior biceps-semitendinosis nerves at group II strength fails to reset the locomotor rhythm (Perreault et al. 1995). Despite the differences in results between preparations, an important concept is that activation of stretch-sensitive afferents in flexors, as it would normally occur during late stance phase of walking, promotes the stance to swing transition.

Alternatively, Duysens and Pearson (1980) proposed that unloading the ankle extensors is an important factor in controlling the transition from stance to swing phase. They found that isometric contraction of more than 40 Newtons (N) in the ankle extensor muscles terminated any rhythmic contraction of ankle extensors and flexors normally observed in locomotion. The occurrence of this phenomenon is independent of the ankle joint position. Ventral root stimulation and large amplitude vibrations, which cause contraction of the ankle extensors, also terminate the alternating flexor and extensor activity (Duysens and Pearson, 1980). These findings led to the idea that force-sensitive Ib afferents in extensors may be involved in controlling the stance to swing transition.

Many subsequent experiments indicated the importance of Ib afferents in the control of stance to swing transition (Conway et al. 1987; Gossard et al. 1994; McCrea et al. 1995; Pearson et al. 1992; Pearson and Collins, 1993; Whelan et al. 1995a; Whelan and Pearson, 1997a). The main finding was that stimulating extensor group I afferents prolonged the period of extensor activity and delays the initiation of the flexor burst. It was suggested that Ib afferents mediate such effects because vibration or low amplitude sinusoidal stretches of the GS muscle, which preferably activate the Ia afferent fibers, are ineffective in prolonging the extensor activity in spinal cats. In contrast, ventral root stimulation, which causes muscle contraction and thus activates the force-sensitive Ib afferents, is effective (Conway et al. 1987; Pearson et al. 1992). However, later experiments indicate that extensor Ia afferents also contribute to the prolongation of extensor activity (Guertin et al. 1995; McCrea et al. 1995). For example, Guertin et al. (1995) reported that in decerebrate cats, small-amplitude vibrations applied to the ankle extensors entrained the locomotor rhythm. In summary, the primary functional implication from these findings is that as the limb is unloaded during late stance phase of walking, the decline in the activity of group Ib afferents causes decreased excitation of the extensors and allows for the initiation of flexor activity.

Studies have also been conducted to investigate whether the same factors such as hip position and load are important in regulating the timing of the stance to swing transition in human walking. Dobkin et al. (1995) claimed that the hip has to be moved into extension to induce spontaneous flexion during treadmill training of spinal cord injured subjects. The importance of hip position in controlling the timing of the stance to swing phase transition, however, has not been experimentally tested in humans.

The effects of load, on the other hand, have been more extensively studied. Finch et al. (1991) found that in normal subjects, the percentage of stance phase was significantly reduced when a body weight support of 30-70% (by raising the subjects via a harness system) was used. Reduction in the percentage of stance phase with reduced load was also reported in spinal cord injured subjects (Visintin and Barbeau, 1989). Unloading by lifting the subjects in a harness actually reduced the distance over which the foot made contact with the treadmill surface. Therefore, the changes in stance phase duration might simply be due to the mechanical effect of unloading.

Other studies examined the effects of increasing the load during walking. Significant increase in the duration of extensor activity was obtained when load was carried in the hand or on the back (Eke-Okoro and Larsson, 1984; Ghori and Luckwill, 1985). However, the stance phase duration was shortened (Eke-Okoro and Larsson, 1984; Ghori and Luckwill, 1985), indicating that postural adjustments were confounding the muscle responses. Although additions in load up to 30% of body weight significantly increased the amplitude of the extensor EMG burst, the step cycle duration did not change (Stephens and Yang, 1999). Only minimal increase in step cycle duration was reported when the load was applied at late stance while the subjects were stabilized by holding a rail (Misiaszek et al. 2000). When the subject was not holding a rail, the loading disturbance significantly increased the step cycle duration. In this case, a postural response with activation of TA muscle was also observed. Thus, the increase in step cycle duration might be due to an attempt to reposition the center of mass forward over the stance leg (Misiaszek et al. 2000). Factors other than loading, such as volitional responses and postural disturbances, might account for the increase in step cycle duration.

Overall, the results in adult humans are weaker and less conclusive than in cats. The differences may be related to a difference in preparation. In adult humans, cortical inputs and many rhythmic sensory inputs during walking may have strong influences on the strength of spinal reflexes. This issue will be discussed in more detail in section 1.8 of this introduction.

The afferent control of stance to swing transition could be mediated by several pathways. Flexor group I and group II afferents have been shown to be effective in entraining the locomotor rhythm (Hiebert et al. 1996), suggesting a pathway from these afferents to the CPG. On the other hand, the excitatory effects on the extensors by stimulation of extensor group I afferents could be mediated by three different pathways. First, the extensor motoneurons could be activated by extensor group Ia afferents via a monosynaptic pathway (Eccles et al. 1957). Second, the feedback excitation of extensors by extensor group I afferents could be mediated by a disynaptic pathway. In decerebrate cats, stimulation of group I ankle or knee extensor afferents during the extension phase gave rise to a short latency EPSP (mean latency: 1.6-1.8ms) in homonymous and heteronymous extensor motoneurons during fictive locomotion, indicating a disynaptic pathway (Angel et al. 1996; McCrea et al. 1995). Third, the fact that activation of extensor group I afferents effectively entrained the locomotor rhythm also suggested the presence of a pathway directly to the CPG. Gossard and colleagues (1994) found that following L-DOPA injection, stimulation of extensor group I afferents evoked a longer latency EPSPs in extensor motoneurons (mean latency: 3.5-4ms), indicating a polysynaptic pathway, probably to the CPG itself.

1.5.3 Reinforcement of extensor activity by sensory input

An important principle in motor control is that ongoing motor activity can be reinforced by afferent feedback (reviewed in Pearson, 1993). Activation of extensor group I afferents during the extensor phase of locomotor rhythm not only delayed the timing of the stance to swing phase transition, but it also increased the amplitude of extensor bursts in reduced preparations of the cat (Conway et al. 1987; Gossard et al. 1994; Guertin et al. 1995; McCrea et al. 1995).

The reinforcing action of afferent feedback on extensor activity was also examined in "foot-in-hole" experiments (Gorassini et al. 1994; Hiebert et al. 1994, 1995). When the foot unexpectedly entered a hole at the beginning of the stance phase, there was substantial reduction of extensor activity. The cat then responded by flexing the hindlimb and lifting the foot out of the hole (i.e. flexion corrective response). It was suggested that the evoked flexion corrective response could be due to the lack of afferent feedback from Ia or Ib afferents which would normally occur during stance phase of walking (Gorassini et al. 1994; Hiebert et al. 1994, 1995). The reduced excitatory effects on the extensor muscles by afferent feedback allows for the subsequent initiation of flexion. Hiebert et al. (1995) found that electrical stimulation of group I afferents as the foot entered the hole preserved the extensor activity and suppressed the flexion corrective response. These findings lend support to the idea that activation of group I afferents enhances the extensor activity during stance phase of walking.

Several studies attempted to quantify the contribution of sensory input to the generation of extensor muscle activity during the stance phase of walking. Severin (1970) reported that the electromyography (EMG) of the triceps surae muscle was reduced by 50% when the fusimotor axons were blocked. Although blockage of some alpha motoneurons could not be ruled out, the results indeed showed that the activity of muscle spindle afferents contribute to generation of muscle activity. Bennett et al. (1996) reported that reflexes contributed to 23% of stretch-related force in the triceps-surae muscle during locomotion in spinal cats. Hiebert et al. (1999) used a few different experimental approaches to estimate the contribution of sensory feedback to the generation of extensor activity in decerebrate cats. First, when the foot unexpectedly entered a hole, the activity of the knee and ankle extensors was reduced by 68-74%. Second, when the ankle extensors were loaded artificially as the foot entered the hole, the magnitude of the ankle extensor activity was considerably increased, similar to that seen during weight-bearing steps. Third, by lifting and dropping the hindquarters of the animal, there was a corresponding reduction and enhancement in knee extensor activity. Finally, transection of L4-L6 dorsal roots eliminated sensory feedback from the quadriceps. As a result, approximately 50% of vastus lateralis EMG was reduced. Similarly, deafferentation of L7-S2 resulted in 56-78% reduction of activity in ankle and knee extensors. Overall, it was estimated that between 50 and 80% of ankle and knee extensor activity was produced by afferent signals (Hiebert et al. 1999).

Using a different experimental approach, Stein et al. (2000) quantified the reflex contribution to the force generation in the triceps surae muscles in walking decerebrate cats. In their preparations, the achilles tendon of one of the hindlimbs was connected to a muscle puller. In some steps, the puller moved the muscle through the pattern of movement that would normally occur during overground walking. In other steps, the puller held the muscle isometrically. By comparing the EMG and force produced during the two different types of steps, it was estimated that about 50% more EMG activity was generated in the triceps surae muscle during E2 part of the simulated stance phase and that 35% of the force over the whole stance phase was produced by stretch-related reflexes (Stein et al. 2000).

The contribution of sensory feedback to generation of extensor activity during stance phase has also been investigated in humans. By electrical means, Stephens and Yang (1996) studied the inhibition produced by stimulating the group I afferents in medial gastrocnemius nerve on the soleus H-reflex. During the stance phase of walking, the inhibition was reduced when compared to standing in healthy subjects (Stephens and Yang, 1996). However, different from the cats (Gossard et al. 1994; Pearson and Collins, 1993; Guertin et al. 1995), no excitation was found (Stephens and Yang, 1996).

Some studies examined the effects of load reduction during walking. In healthy subjects, Finch et al. (1991) reported a significant reduction of leg extensor EMG amplitude during stance phase of walking when body weight support was provided via a harness, with the most reduction in amplitude (>50%) occurring in gastrocnemius muscle with 70% body weight support. Similar findings were also reported in spinal cord injured subjects (Visintin and Barbeau, 1989). Other studies examined the effects of adding load. With sustained or transient loading up to 30% body weight was applied during treadmill walking, the EMG amplitude of ankle extensor and knee extensor was significantly increased (Stephens and Yang, 1999). As much as 134% increase in vastus lateralis activity was reported during the early stance phase when the load was unexpectedly added (Stephens and Yang, 1999). By applying transient load along the long axis of the leg at the end of the stance phase, significant increase in extensor activity was obtained (Misiaszek et al. 2000). In both normal and spinal cord injured subjects, a positive correlation between load and soleus or medial gastrocnemius EMG amplitudes was identified at load levels of <50% of the body weight (Harkema et al. 1997). These results suggested that the sensory information associated with loading played a role in reinforcing ongoing extensor activity during stance phase of walking.

Other studies attempted to quantify the contribution of afferent feedback to the generation of extensor EMG activity during human walking. By using a pneumatic device to apply small, rapid stretches to the soleus muscles during stance phase of walking in adult humans, Yang et al. (1991) estimated that Ia afferents contributed 30-60% to the activation of the soleus EMG signal during the early part of the stance phase. Sinkjaer et al. (2000) reported that when the ankle extensors were unloaded by using a portable stretch device, the soleus activity was reduced to 50% in early and mid-stance. It was suggested that such EMG enhancing action was mediated by group II or group Ib afferents because ischemia in the leg, which abolished the group Ia short latency reflex, did not change the result. Later, Grey et al. (2001) found that the amplitude of the medium latency soleus stretch reflex during stance phase of walking was not changed by ischemia. However, after ingestion of tizanidine, a drug known to depress transmission in group II afferent pathways, the medium latency reflex component of the soleus stretch reflex was significantly reduced. Therefore, the authors suggested that the reinforcement of soleus EMG during stance phase is mediated by group II afferents. However, tizanidine may have actions on other reflex pathways (e.g. Ib, cutaneous afferents). Therefore, these findings do not rule out possible contribution of Ib pathways to the generation of the medium latency reflex component of soleus EMG during stance phase (Grey et al. 2001).

In summary, not all of the extensor muscle activity generated during walking is produced by the CPG. Sensory feedback also plays a significant role in generating muscle activity during walking. In particular, the activation of group I and II afferent fibers during stance phase of walking results in reinforcement of extensor activity. Such augmentation of extensor activity is important to counteract the load imposed on the stance limb during walking, so as to avoid collapse of the weightbearing leg.

1.5.4 Interlimb coordination

Stability in walking requires good coordination of movements between the limbs involved. Normally, one leg must achieve ground support when the other leg is initiating the swing phase in a biped, thereby preserving equilibrium. Grillner and Rossignol (1978) found in chronic spinal cats that although the hip was extended sufficiently, the initiation of the swing phase often did not occur until the contralateral side reached mid-stance or mid-swing phase. It was suggested that the former response corresponded to alternating gaits such as a trot or a walk while the latter resembled in-phase stepping such as a gallop (Grillner and Rossignol, 1978). In decerebrate cats, the latency for the initiation of flexor activity induced by stretching the iliopsoas muscle was longer if the stretch occurred during contralateral flexor activity than during contralateral extensor activity (Hiebert et al. 1996). Thus, the initiation of the swing phase does not only depend on the sensory input to the ipsilateral leg, but also on the state of the contralateral limb.

Disturbances that prolong the swing phase also cause compensatory reactions in the contralateral limb in order to preserve stability. In adult humans, when the swing phase was briefly interrupted by resisting the forward movement of the swinging leg, the stance phase and extensor EMG burst durations of the contralateral limb were prolonged (Dietz et al. 1986). The corrective response during stumbling is another good example. In both cats (Forssberg et al. 1977; Matsukawa et al. 1982) and humans (Eng et al. 1994; Schillings et al. 2000), after the dorsum of the foot hit an obstacle, coordinated muscle activity was evoked. As a result, the swing phase of the perturbed leg and the stance phase of the contralateral leg were both prolonged.

Other experimental evidence also showed that the homologous limb pairs were extremely coordinated despite the application of various forms of perturbations. In cats, when the ipsilateral limb entered a hole during contralateral swing phase, the corrective flexion response of the disturbed limb was delayed until the contralateral limb regained ground contact (Gorassini et al. 1994; Hiebert et al. 1994). If the ipsilateral limb entered the hole during contralateral stance phase, the stance phase of the contralateral leg was prolonged until the ipsilateral limb regained ground contact (Gorassini et al.1994; Hiebert et al. 1994). In 'split-belt' experiments, the 1:1 rhythm of the two hindlimbs was largely maintained despite that the two belts ran at very different speeds. Similar results have been reported in intact (Halbertsma, 1983), decerebrate (Kulagin and Shik, 1970) and spinal cats (Forssberg et al. 1980b) as well as human adults (Dietz et al. 1994; Prokop et al. 1995) and infants (Thelen et al. 1987). Thus, there must be some mechanisms in the CPG which co-ordinate the step cycle durations of the two limbs by utilizing the afferent feedback signals from each leg (Halbertsma, 1983). These findings also seem to support the CPG model used in Hiebert et al. (1996), which is adapted from the half-centre model by Brown (1911). In their model, the flexor half-centers on each side mutually inhibit each other, in agreement with the findings that the initiation of the swing phase (flexor activity) on one side is usually accompanied by the stance phase (extensor activity) on the other side (Hiebert et al. 1996). In addition to the spinal mechanisms, certain brainstem pathways seem to be involved in maintaining interlimb coordination and equilibrium during locomotion, including the reticulospinal tract and vestibulospinal tract. Lesions of the ventral and ventrolateral funiculi of the spinal cord in the cat, which cause extensive damage to the vestibulospinal and reticulospinal tracts, lead to severely disrupted interlimb coordination and poor lateral stability (Brustein and Rossignol, 1998). Intact sensory input is also important for maintaining good interlimb coordination, since it has been shown that reduction of sensory inflow disrupts interlimb coordination during walking (Allum et al. 1998; Giuliani and Smith, 1987; Grillner and Zangger, 1979).

1.6 Gating of sensory input to the locomotor pattern generator

As discussed in previous sections, the CPG is subject to powerful influence from afferent signals. The effects of the same sensory input on the locomotor pattern, however, vary with different tasks or different phases of a task (reviewed in Rossignol, 1996). For example, in the cat, the same cutaneous stimulation to the paw results in different responses during different directions of walking (Buford and Smith, 1993) or during different parts of the step cycle (Forssberg et al. 1975, 1977). In adult humans, the amplitude of soleus H-reflex increases as the subject goes from running to walking and to standing (Capaday and Stein, 1986, 1987). The task-dependent and phase-dependent reflex responses indicate that the reflex transmission of afferent pathways to the CPG is continuously modulated. The CPG is capable of gating the sensory inflow to the CPG itself (reviewed in Pearson and Ramirez, 1997; Prochazka, 1989). Such sensory gating allows the generation of reflex responses appropriate for the behavioral state of the animal (Pearson, 1993).

There are at least four levels at which the modulation of spinal reflexes can take place during locomotion (reviewed in Rossignol, 1996; Orlovsky et al. 1999). First, the modulation could occur at the level of the sensory receptors. One of the mechanisms involves efferent modulation of proprioceptors by gamma motoneurons (reviewed in Orlovsky et al. 1999; Prochazka, 1989). The behavior of the muscle spindle afferents could be greatly influenced by the changes in fusimotor action. For example, in cats, the stretch-sensitivity of the ankle extensor spindle primary ending is markedly elevated during pouncing on a moving toy as compared to that during normal stepping (Prochazka, 1989). Phase-dependent modulation of the activity of muscle spindle afferents by gamma motoneurons has also been reported in various preparations of the cat (Cabelguen, 1981; Cabelguen et al. 1984; Loeb and Duysens, 1979; Murphy et al. 1984; Perret and Buser, 1972; Prochazka and Gorassini, 1998a,b). Direct recordings from the gamma motoneurons of the ankle extensor muscles show a fluctuation of the firing of the static and dynamic gamma motoneurons with the locomotor cycle (Murphy et al. 1984; Taylor et al. 2000). These data indicate that the CPG is capable of modulating the efficiency of transmission of spinal reflex pathways by its phasic influences on the gamma motoneurons (reviewed in Orlovsky et al. 1999).

Second, reflex modulation could be caused by the phase-dependent changes of the membrane potential of alpha motoneurons. In cats, intracellular recordings showed that motoneurons innervating various hindlimb muscles during fictive locomotion underwent one depolarization and one repolarization in each locomotor cycle. The repolarization could be reversed by chloride injection into the motoneuron, suggesting the presence of inhibitory input onto the motoneurons (Orsal et al. 1986). Shefchyk and Jordan (1985) also provided direct evidence that various hindlimb alpha motoneurons received EPSPs and IPSPs produced by stimulation of the mesencephalic locomotor region (MLR). These postsynaptic potentials were modulated in amplitude during the locomotor cycle so that the EPSPs were largest during the depolarized phase of the step cycle and replaced by IPSPs during the hyperpolarized phase (Shefchyk and Jordan, 1985). These results indicated that the motoneurons receive rhythmic excitatory and inhibitory inputs, suggesting that the CPG modulates the membrane potential and hence the excitability of the motoneurons in a phase-dependent manner. As a result, the strength of the reflex is higher when the afferent is activated at a time when the motoneuron is more excitable, a phenomenon called "automatic gain compensation" by Matthews (1986).

Third, the modulation of spinal reflexes could occur at a premotoneuronal level. In *Xenopus* embryos, sensory inputs from skin receptors were effective in causing a reflex bending of the body away from the stimulus only at certain phases of the swimming cycle. Such gating of sensory information was caused by rhythmic inhibition on the sensory interneurons by the CPG for swimming (Sillar and Roberts, 1988). In cats, responses of reciprocal Ia inhibitory interneurons were also subject to modulation from the locomotor CPG (Feldman and Orlovsky, 1975). During MLR-evoked locomotion in decerebrate cats, the activity of reciprocal Ia inhibitory interneurons (IaINs) was synchronous with the muscle which supplied them with Ia afferent input. For example, the quadriceps IaINs were mainly active during the extensor phase of the step cycle (Pratt and Jordan, 1987). Moreover, the quadriceps IaINs were activated by stimulation of the quadriceps nerve only during the extensor phase of locomotion (Feldman and Orlovsky, 1975). Through the control of excitability of IaINs, the CPG could thus change the efficiency of the transmission of Ia sensory input to itself (Feldman and Orlovsky, 1975). Furthermore, in some cases, the same afferents might have synaptic connections with different groups of interneurons. Depending on the task or the phase of the task, the gains of these different pathways were selectively altered (Andersson et al. 1978). For example, disynaptic IPSPs were evoked in extensor motoneurons by stimulation of extensor group I afferents at rest (non-reciprocal group I inhibition). In contrast, the same stimulation evoked disynaptic EPSPs during locomotion (McCrea et al. 1995). Presumably, the group I afferents had synaptic connections to both the excitatory and the inhibitory interneurons. The reflex reversal during locomotion indicated that the activation of locomotor network produced different effects on the two groups of interneurons (i.e. inhibiting the inhibitory interneurons and activating the excitatory interneurons) (McCrea, 1998). The change from inhibitory to excitatory effects on extensor motoneurons by stimulation of extensor group I afferents during locomotion accounts for the reinforcement of extensor muscle activity during stance phase of walking. Such a reflex response is functionally appropriate because the increased extensor activity minimizes distortions in the kinematic pattern as the limb is loaded during the stance phase of walking (Orlovsky et al. 1999).

Finally, the phasic modulation of reflexes could occur at a presynaptic level. In humans, the H-reflex amplitude decreased as the subject switched from standing, walking and to running despite that the EMG amplitude was matched between these tasks. Because the H-reflex is likely mostly monosynaptic, it was suggested that the modulation of H-reflex might be related to presynaptic mechanisms (Capaday and Stein, 1986, 1987). The presynaptic events in sensory neurons could be recorded intracellularly from sensory neuron axonal terminals as primary afferent depolarizations (PADs) or extracellularly as dorsal root potentials (reviewed in Nusbaum et al. 1997). Ample evidence showed that the CPG also controlled the sensory input through presynaptic mechanisms. Sensory axon terminals from leg joint proprioceptors in crayfish received primary afferent depolarizations that were time locked to the locomotor rhythm (Cattaert et al. 1992; El Manira et al. 1991). During fictive locomotion in decorticate and spinal cats, the dorsal root potentials showed oscillations of depolarizations which fluctuated at the locomotor rhythm (Baev, 1981; Baev and Kostyuk, 1982; Gossard and Rossignol, 1990). In axonal terminals of cutaneous afferents, the membrane potential oscillated at the rhythm of the fictive locomotion in decorticate, mesencephalic and low spinal cat, indicating that the CPG modulated the polarization of afferent terminals (Gossard et al. 1989). In addition, stimulation of cutaneous or muscle nerves in the hindlimbs could also evoke dorsal root potentials that were phasically modulated, indicating that transmission of spinal reflex pathway could also be modulated by movement-related feedback during real locomotion (Gossard and Rossignol, 1990). Evidence in crayfish and cats showed that the presynaptic inhibition of afferent terminals was mediated by gamma-aminobutyric acid (GABA) (Cattaert et al. 1992; reviewed in Rudomin and Schmidt, 1999). Through presynaptic inhibition on the afferent terminals, the CPG can selectively alter the strength of the transmission of different reflex pathways. Such gating of sensory information ensures that reflexes are appropriate as the behavioral state of the animal changes (reviewed in Pearson, 1993).

1.7 Adaptation to sustained changes in sensory input during locomotion

1.7.1 Adaptation to sustained reduction of sensory input

Transient sensory inputs have been shown to potently influence the operation of the locomotor CPG. But how does the locomotor pattern adapt to sustained alterations in sensory input? Different experimental approaches have been conducted to examine this issue. One approach to study this subject is to reduce the sensory input by hindlimb deafferentation (Goldberger, 1977; Goldberger and Murray, 1982; Zhang et al. 1995). Immediately after deafferentation of one hindlimb in otherwise intact cats, locomotion was severely impaired. The walking pattern was characterized by abnormal limb excursions, misplacement of the paw and reduced speed. Some animals even used a 3-legged walking pattern in which the deafferentated limb did not bear any weight. However, as time progressed, the animal continued to show improvement. Approximately 3 weeks after deafferentation, the affected limb displayed an almost normal locomotor pattern (Goldberger, 1977).

What are the underlying adaptive mechanisms to allow for the recovery of function? Goldberger (1977) found that after recovery from hindlimb deafferentation, ipsilateral hemisection at the level of the 1st lumbar (L1) segment abolished the recovery, indicating that the ipsilateral descending systems might be involved in the recovery of locomotion. Anatomical studies confirmed the presence of sprouting of ipsilateral descending projections (Goldberger, 1977; Goldberger and Murray, 1982). Additionally, the remaining dorsal roots might also contribute to the functional recovery. Sparing of one lumbar root reduced the original locomotor deficit in the partially deafferented hindlimb and allowed the animal to recover faster than the cats with complete lumbosacral deafferentation (Goldberger, 1977). These observations paralleled the anatomical findings that sprouting of the spared lumbar root and low thoracic roots occurs in these animals (Goldberger, 1977; Goldberger and Murray, 1982; Zhang et al. 1995).

Other researchers studied the plastic changes in locomotor reflex pathways following selective neurectomy. It has been reported that stimulation of group I afferents in ankle extensors are effective in prolonging the stance phase in decerebrate cats (Whelan et al. 1995a). Moreover, the effect of lateral gastrocnemius/soleus (LGS) stimulation was much larger than that of medial gastrocnemius (MG) stimulation. However, following axotomy of the LGS nerve, the effectiveness of the LGS group I afferents in prolonging the cycle period was markedly reduced starting at 3 days after axotomy. In contrast, the effectiveness of the synergist MG group I afferents was significantly increased at 5 days after axotomy (Whelan et al. 1995b; Whelan and Pearson, 1997b). Subsequent experiments examined the effects of selective neurectomy on the kinematics and the muscle activity in the spared MG muscle. Immediately following LGS axotomy, there was a large increase in ankle yield. Abnormal stretch to the MG muscle also led to an increase in amplitude of the MG bursts. As time progressed, the ankle yield was gradually reduced, accompanied by an increase in the amplitude of the MG EMG bursts (Pearson et al. 1999). Similar functional recovery was also observed following temporary weakness induced by injecting botulinum toxin into the ankle extensors except the MG muscle (Misiaszek and Pearson, 2002). These experimental findings demonstrated the tremendous ability of the animal to adapt the locomotor pattern to sustained reduction of sensory input, whether it be induced by nerve transection or chemically induced muscle weakness.

A question that arises from these studies is where the adaptive plasticity occurs. The changes in effectiveness of LGS and MG group I reflex pathways persisted after a complete transection of the spinal cord in some animals, indicating that at least one site of plasticity is within the spinal cord (Whelan and Pearson, 1997b). The functional recovery (i.e. reduction in ankle yield and increase in MG muscle activity) following LGS nerve transection has also been reported in chronic spinal cats (Bouyer et al. 2001), again confirming that the spinal cord is capable of adaptive locomotor plasticity following nerve injury.

Interestingly, the functional recovery depends on the use of the leg (Pearson et al. 1999). If the denervated leg was immobilized, no decrease in ankle yield and increase in the amplitude of MG bursts occurred at 7 days after nerve transection (Pearson et al. 1999). These results strongly indicated that afferent feedback generated during walking contributes to the recovery (Pearson et al. 1999). However, as the early component of ankle extensor activity was generated centrally (Gorassini et al. 1994), it is likely that the adaptive plasticity also involved changes in central drive (Pearson et al. 1999). Involvement of supraspinal structures in locomotor plasticity following neurectomy was confirmed in the study by Carrier et al. (1997). If the cat was spinalized first before the ankle flexors were neurectomized, the locomotor pattern returned to almost normal within a few days. It indicates that the spinal cord on its own is capable of plastic functional change. On the other hand, after adaptation to ankle flexor neurectomy, a subsequent complete spinal transection revealed a disorganized locomotor pattern. Hyperflexion of the knee and absence of plantar foot contact were observed. The difference in results between the two groups of cats indicated that when neurectomy preceded spinal transection, supraspinal signals were generated to compensate for the peripheral deficit, which in turn produced changes in the spinal cord over-time. Removing the supraspinal input by spinalization revealed the somewhat disorganized pattern generated by spinal mechanisms without descending compensation (Carrier et al. 1997).

In summary, despite marked reduction of sensory information, substantial recovery in locomotor function could take place. Adaptive plasticity in the nervous system occurs at different levels of the nervous system, allowing the animal to compensate for peripheral deficits.

1.7.2 Adaptation to sustained externally applied perturbations

Sustained changes in the locomotor environment can pose a significant challenge to the successful achievement of the animal's behavioral goal. Real locomotion requires the ability to adjust the walking pattern to a changing environment, such as walking uphill or downhill, changes in terrain, presence of obstacles and changes in the body, such as growth of the musculoskeletal system and fatigue in muscles. How does the nervous system deal with sustained alterations in the external environment during walking? In decerebrate ferrets and cats, when the swing phase is perturbed by an obstacle, the animal increases the maximal height of the limb during swing phase to avoid the obstacle after several perturbed steps. Interestingly, upon removal of the obstacle, the high stepping persists for several step cycles (i.e. after-effect), indicating that learning has taken place (Lou and Bloedel, 1987; Bloedel et al. 1991). Similar phenomenon has also been reported in spinal cats (Edgerton et al. 2001; Hodgson et al. 1994).

After-effects have also been observed in human subjects during locomotor tasks. For example, after jogging on treadmill for a period as short as 60 seconds, the blindfolded subjects jogged forward on solid ground when told to jog in place (Anstis, 1995). In another example, following a period of walking on the perimeter of a rotating disk, the subjects continued to show a curved locomotor trajectory overground when blindfolded although they were told to step on the floor in a straight line (Gordon et al. 1995; Weber et al. 1998). Such after-effects were also seen following unilateral hopping, slope walking (Anstis, 1995) and walking on a split-belt treadmill (Jensen et al. 1998). A recent study has also shown that following a period of walking with a cuff weight attached to the lower leg, some human infants demonstrate after-effects (i.e. high steps) immediately after removal of the weight (Lam et al. 2003). Interestingly, the learning effects seen in split-belt locomotion or unilateral hopping did not transfer between the two legs, indicating that specific afferent input of the respective legs was necessary for this form of learning (Anstis, 1995; Jensen et al. 1998). In contrast, during learning of repetitive stepping over an obstacle, the motor skill could be transferred to the mirror condition in which the contralateral leg became the leading leg in the step over the obstacle (van Hedel et al. 2002). These results showed that the human nervous system is able to learn following exposure to sustained changes in external conditions. The after-effects observed after the removal of the perturbations reveal the compensatory strategies employed to counteract the effects of the perturbations.

While both lower animals and humans show ability to learn in response to sustained changes in the locomotor environment, exactly where these plastic changes occur remains unclear. The fact that decerebrate ferrets show after-effects following repeated perturbations to the swing phase suggests that adaptive locomotor plasticity could occur without the cerebrum (Lou and Bloedel, 1987). Decerebrate-decerebellate ferrets also demonstrate such after-effects, indicating that the cerebellum is not essential for this type of learning (Bloedel et al. 1991).

Cerebellum was also implicated to play an important role in learning in the context of locomotion by other researchers. After decerebrate cats were placed on a split-belt treadmill which can drive the limbs at different speeds, they slowly learned to adjust the step cycle of each leg. The step cycle of each leg eventually attained a stable value. With repeated trials, the time it took for the step cycle to reach the stable value became less, indicating the presence of learning (Yanagihara and Kondo, 1996). Increase in complex spike discharges from the Purkinje cells in the cerebellum were also obtained during split-belt locomotion (Yanagihara and Udo, 1994). This learning, however, was abolished in decerebrate cats when synthesis of nitric oxide was inhibited in the vermis (Yanagihara and Kondo, 1996). This in turn inhibited the formation of long term depression (LTD) of synapses from parallel fibers onto the same Purkinje cells. This LTD in the cerebellar cortex was thought to play a key role in motor learning (Gilbert and Thach, 1977; Ito, 1989; Marr, 1969; Yanagihara and Kondo, 1996). In humans, patients with cerebellar lesions also showed inconsistent adaptive responses when exposed to repeated changes to treadmill speed during walking (Rand et al. 1998). A recent study also found that patients with cerebellar degeneration showed impaired podokinetic adaptation (Earhart et al. 2002b).

In summary, both animal and human data seem to support the idea that the cerebellum is important for certain types of adaptive locomotion. This is not surprising, since other experiments studying non-locomotor tasks also showed that the cerebellum was involved in motor learning (Imamizu et al. 2000; Martin et al. 1996a, b; Nezafat et al. 2001; Thach et al. 1998). The specific cerebellar pathways involved in various types of learning during adaptive locomotion requires further study.

1.8 Using the human infant as a model to study sensory control of walking

1.8.1 Differences between reduced preparations of the cat and adult humans in response to sensory input during walking

Sensory control of locomotion has been extensively studied in the cat. There is evidence that the strength of the effects of certain sensory inputs depends upon the specific preparations used. For example, the effects of the activation of the load-sensitive receptors in the extensor muscles were much stronger in the decerebrate cat than in the intact cat (Whelan et al. 1995a; Whelan and Pearson, 1997a). The difference in results may reflect the different amount of cortical influence on the spinal and brainstem circuitry for walking.

Certain sensory inputs that evoked robust responses in reduced preparations of the cat produced very modest responses in adult humans. For example, increased load on the extensor muscles consistently increased the duration and amplitude of the extensor muscle EMG burst in the reduced preparations of the cat (Conway et al. 1987; Gossard et al. 1994; McCrea et al. 1995; Pearson and Collins, 1993; Whelan et al. 1995a). In adult humans, however, addition of load only increased the extensor EMG amplitude, but did not significantly increase the step cycle duration (Misiaszek et al. 2000; Stephens and Yang, 1999). While vibration of certain hindlimb muscles caused significant changes in the structure of the step cycle in the reduced preparation of the cat (Guertin et al. 1995; Hiebert et al. 1996), bursts of vibration to the lower leg muscles during walking had little effect in humans (Ivanenko et al. 2000). Similar to the situation in the cat, the modest effects demonstrated in the adult humans may be related to the large amount of cortical input to the spinal locomotor circuitry.

Cortical inputs can exert powerful influences on the functioning of the neural circuitry in the lower centers of the nervous system. For example, many pyramidal tract neurons in the motor cortex increased their discharge during voluntary gait modification to avoid an obstacle (Drew, 1991; 1993). Resetting of the locomotor cycle could also be achieved by microstimulation of the motor cortex (Drew, 1991; Orlovsky, 1972). These results indicated that the motor cortex could control the timing and amplitude of muscle activity. In addition, volition could interfere with how the subcortical locomotor circuitry responds to sensory information. Therefore, while it is possible that the differences in results between adult humans and spinal / decerebrate cats may reflect a fundamental difference between the two species, it is equally possible that the different results may be due to a difference in preparations. In order to answer this question, a human model in which the spinal and brainstem locomotor circuitry is less subject to cortical influences is required.

1.8.2 Stepping response in human infants

One method to study the behavior of the locomotor CPG in humans is to use complete spinal cord injured subjects. However, spontaneous stepping movements in these patients are extremely rare. Even following intensive training, no stepping movements can be performed without assistance (Dietz et al. 1995). Moreover, ample plastic changes can take place in the spinal cord following injury or training. These changes could potentially affect how the spinal locomotor circuitry responds to sensory inputs. In order to study how the healthy human locomotor circuitry controls walking, a human infant model has been developed (Yang et al. 1998).

Human infants demonstrate a stepping response from birth (McGraw, 1940; Peiper, 1929; Zelazo, 1983). In fact, the human fetus shows well-coordinated stepping-like movements *in utero* as early as 10 weeks of gestation (de Vries et al. 1984). The stepping response in infants is thought to be controlled by the spinal cord and brainstem because anencephalic infants demonstrate similar stepping movements (Peiper, 1963). The infant stepping pattern, however, differs from adult walking in many aspects. One of the main differences is that infant stepping is characterized by a digitigrade pattern as opposed to the plantigrade pattern in adult walking. Interestingly, as the child becomes independent in walking, the gait pattern continues to be digitigrade until the later part of the second year (Forssberg, 1985). Such a gradual change from the infantile stepping pattern to a mature adult stepping pattern led Forssberg (1985) to suggest that the stepping movements in infants and independent locomotion are controlled by the same pattern generator in the spinal cord. Human infants may thus serve as an excellent model for the study of subcortical control of human walking. Results from histological, radiological and electrophysiological data all lend support to the idea that while parts of the brainstem and spinal cord are quite mature at birth, the descending pathways from the motor cortex are far from mature. In the following sections of this introduction, the maturation of the peripheral nervous system (PNS) and central nervous system (CNS) will be discussed.

1.8.3 Development of the peripheral nervous system

From a functional point of view, the PNS is capable of mediating reflexive movements in a very early stage of prenatal life. The first muscles become innervated by the alpha motoneurons by 5-6 gestational weeks (GW) (Lang et al. 1988). The first spontaneous movements can be observed as early as 6.5 weeks in utero (Altman and Bayer, 2001). The earliest closure of reflex arc occurs a week later (Altman and Bayer, 2001). Direct observations of movements in aborted fetuses revealed that orofacial reflexes could be elicited by cutaneous stimulation (by touching or stroking with hair esthesiometers) of the skin area supplied by the trigeminal nerve at approximately 7.5 weeks (Humphrey, 1964). The development of the cutaneous reflexes then spreads to more distal regions such as the palms of the hands and the soles of the feet (Humphrey, 1964). Incomplete closure of all fingers can sometimes be evoked by cutaneous stimulation to the palm of the hand at 10 - 10.5 weeks. Cutaneous stimulation to the sole of the foot can also elicit dorsiflexion of the great toe and toe fanning at 10.5 - 11 weeks (Humphrey, 1964). In summary, the PNS can be considered to be capable of functioning at the most basic level as early as the first trimester (Lang et al. 1988).

During the early stages of development, the innervation of muscle fibers is polyneural (Gramsbergen et al. 1997). In other words, a single muscle fiber is supplied by multiple axons from different motoneurons. For example, in a fetus of 15.5 weeks post menstrual age, the muscle fibers are innervated by an average of 2 axons per motor endplate, although as many as 5 axons per endplate are observed in some muscle fibers. This pattern of polyneural innervation persists until 25 weeks of postmenstrual age, after which a gradual regression of polyneural innervation occurs. The muscle fibers become predominantly mononeurally innervated from approximately 12 weeks post term, just as in adults (Gramsbergen et al. 1997).

The sensory nerve endings are developed in a very early stage in the human fetus. For example, the first evidence of muscle spindle formation can be found in biceps brachii as early as 11 GW, with the nerves beginning to form distinct motor and sensory connections with the striated muscle fibers (Cuajunco, 1940). Muscle spindles can be found in practically all muscles by the 4th month of fetal life and their maximal fetal development (i.e. increase in number and diameter of intrafusal muscle fibers, myelination of nerve fibers, morphological maturation of the capsule, etc.) occurs between the 24th and 31st GW (Cuajunco, 1940; Humphrey, 1964). Other sensory nerve endings also begin their development early in utero. For example, the formation of Pacinian corpuscle in the palmar surface of the hand starts at approximately 12 GW (Cauna and Mannon, 1959). This coincides with the time when cutaneous stimulation of the hand consistently elicits incomplete finger closure of all fingers (Humphrey, 1964). Definitive Merkel's corpuscles and Meissner's corpuscles in the same region can be identified by 16.5 GW and 24-28 GW, respectively (Hewer, 1935; Szymonowicz, 1933). Thus, all proprioceptive and cutaneous sensory nerve endings found in the adult are represented in the newborn infant, although the structures of the specialized receptors are not as complicated as in adults (Humphrey, 1964). The results also indicate that complete maturation of the sensory nerve endings is not essential to the expression of fetal cutaneous reflexes.

The development of the ventral nerve roots is more advanced than the dorsal roots. Myelination of the proximal ventral root is already in progress by 20 GW and advanced myelination can be observed as early as 26 GW (Altman and Bayer, 2001). In contrast, the myelination of the dorsal root sensory fibers is not evident until 32 - 33 GW (Altman and Bayer, 2001). The development of the ventral nerve roots also terminates earlier than the dorsal nerve roots. For example, the ventral nerve roots in the lumbar region acquire the adult morphological appearance at the age of 2 to 5 years (Lang et al. 1988; Rexed, 1944). The dorsal roots in the lumbar region, on the other hand, do not achieve their full development until between 5 and 9 years of age (Lang et al. 1988; Rexed, 1944). The number of myelinated fibers continues to increase in the nerve roots during the postnatal development, and caliber spectrum analysis reveals a maximum of 2 to 5 μm at the level of the 1st sacral ventral root in the newborn (Rexed, 1944). With maturation, a bimodal distribution with a second maximum of 8 to 9 μm is noted at the age of 8 years, just as in the adult (Rexed, 1944). The morphological maturation of the nerve roots, therefore, is not completed until the second part of the first decade of postnatal life (Lang et al. 1988).

The peripheral nerves also undergo a protracted course of maturation. At birth, few myelinated fibers were present in various peripheral nerves in the upper and lower extremities. About half of the fibers become myelinated at the age of 2.5 years and the adult pattern is reached at 9 years (Cottrell, 1940). At 5 years of age, the mean axonal diameter and the number of large-diameter axons of the sural nerve show a twofold and threefold increase, respectively, when compared with 5 month-old fetuses

(Schroder et al. 1978). Similar to the nerve roots, the frequency distribution of the nerve fibers shows a unimodal distribution with a maximum of 2-3 μm in the newborn. The bimodal distribution is already starting to appear in 7 months. An adult profile with a second maximum of 9-10 μm is noted at around 5 years of age (Gutrecht and Dyck, 1970). Axons with a larger diameter have thicker myelin sheath and longer internodal length whereas axons with a smaller diameter have thinner myelin sheath and shorter internodal length (Gutrecht and Dyck, 1970; Schroder et al. 1978). Both the thickness of the myelin sheath and the axonal diameter show a rapid increase between birth to 5 years of age. Thereafter, the thickness of the myelin sheath continues to increase until about 14 years of age. In contrast, the axonal diameter gradually decreases to reach the adult value at 14 years of age (Lang et al. 1988; Schroder et al. 1978). This asynchronous development of myelination and axonal diameter may partially explain the results from electrophysiological studies examining the nerve conduction velocity in children, which will be discussed below (Schroder et al. 1978).

Maximal nerve conduction velocity provides a picture for the maturation of the thickest population of axons in a peripheral nerve (Lang et al. 1988). Basically, the conduction velocity increases with conceptional age (Schulte et al. 1968). The conduction velocities of various peripheral nerves in the upper and lower extremities at birth are about half of those found in normal adults. At about 5 years, these velocities reach adult values (Eisengart, 1970; Schulte et al. 1968; Thomas and Lambert, 1960; Vecchierini-Blineau and Guiheneuc, 1979). By using a variety of techniques such as electromagnetic stimulation of the nerve roots and recording of somatosensory evoked potentials, it was found that the conduction delays in the peripheral components of both motor and somatosensory pathways decreased initially from birth to 5 years. From the age of 5 years on, the conduction delays progressively increased in proportion to the length of the upper or lower extremity. The results thus indicate that the fiber diameter and conduction velocity of the peripheral nerves reach their maximum value at about 5 years (Eyre et al. 1991; Muller et al. 1991). This is consistent with the findings from histological studies, which showed that the overall caliber (axon plus myelin sheath) of the myelinated nerve fibers reach the adult value at the age of 5 years (Schroder et al. 1978).

1.8.4 Maturation of the spinal cord

Ample evidence indicates that the human spinal cord is quite mature at birth. Growth-associated protein (GAP-43) expression is associated with neurite outgrowth and has been used to study the development of the human spinal cord (Eyre et al. 2000). GAP-43 immunoreactivity is prominent throughout the spinal cord at 24-25 weeks of postconception age. At 30-33 weeks post conception age, the expression of GAP-43 is greatly reduced except in the corticospinal tract, which continues to show strong immunoreactivity for GAP-43 (Eyre et al. 2000). These findings indicate that all the major fiber tracts in the spinal cord have completed their growth phase of development by 33 weeks postconception age, with the exception of corticospinal tract (Eyre et al. 2000). This is consistent with the findings in lower animals, where descending spinal projections from the brainstem are present in the spinal cord at very early stages (Clarac et al. 1998; Leong et al. 1984; Martin et al. 1982; Okado and Oppenheim, 1985).

Myelination is often used as an indicator of functional maturation in the developing nervous system (Brody et al. 1987). Myelination in the human central nervous system begins at mid-gestation. It starts from the spinal cord and proceeds cephalad (Holland et al. 1986; McArdle et al. 1987; Sie et al. 1997). The myelination of spinal nerve roots is initiated at a very early stage at 20-22 GW, followed by sensory tracts and extrapyramidal system. The myelination of major motor tracts at the level of the spinal cord, in contrast, is not initiated until the third trimester (Langworthy, 1933; Larroche, 1977; Yakovlev and Lecours, 1967). Myelin Basic Protein (MBP), which constitutes about 30% of total myelin protein, has been used to indicate the degree of myelination of human fetal spinal cord. By 12 gestational weeks, MBP expression is observed in all three funiculi of the cervical and the lumbar spinal cord. The intensity of MBP expression continues to increase so that by 24 GW, MBP expression is prominent throughout the white matter of the spinal cord so that no specific functional tracts could be identified based on the variation in the MBP expression, except the unmyelinated lateral corticospinal tracts (Grever et al. 1996; Weidenheim et al. 1992, 1996). Other experiments use proteolipid (PLP; 50-60% of total protein of myelin) and myelin-associated protein (MAG; 1% of myelin protein) to study the myelination process of the human fetal spinal cord. The results are very similar except that the expression of MBP preceded that of PLP and MAG by about 2 weeks (Weidenheim et al. 1996). In agreement with the above results, the fetal spinal cord shows rare, noncompacted myelin lamellae at 12 GW under electron microscopy (Grever et al. 1996; Weidenheim et al. 1992). At 24 GW, compact myelin throughout the white matter of the spinal cord is observed, with the exception of the unmyelinated corticospinal tract (Grever et al. 1996).

Other experiments study the receptor expression of the fetal spinal cord. In the third trimester fetal spinal cord, high levels of alpha-amino-hydroxy-5-methyl-4-isoxazole proprionate (AMPA), kainate, and NMDA receptors are already established throughout the spinal gray matter. The level of the expression of the three types of ionotropic glutamate receptors is gradually reduced until the adult pattern is established at about 3-4 months postnatally for AMPA receptors, 2 years for kainate receptors, and 1-2 months for NMDA receptors (Kalb and Fox, 1997). These results indicate that glutaminergic receptor expression quickly adopts an adult pattern within the 1st postnatal year. Glutaminergic agents can powerfully initiate locomotor activity in many other animal species (Cheng et al. 1998;

Clarac et al. 1998; Douglas et al. 1993; Matsushima and Grillner, 1992). For example, the reticulospinal tract neurons in the lamprey release glutamate and activate the spinal locomotor network (Buchanan et al. 1987; Grillner, 1996; Grillner et al. 1998). Based on the presence of well myelinated descending fiber tracts in the spinal cord (except the corticospinal tract) and the adult-like pattern of glutaminergic receptor expression in infants, it is reasonable to assume that the spinal locomotor circuitry in infants under the age of 1 is subject to substantial control of descending pathways from the brainstem.

1.8.5 Maturation of the brainstem

Available data indicate that the human brainstem is functionally mature at birth. Morphometric studies indicate that the brainstem undergoes the greatest maturation during the fetal period (Dambska and Kuchna, 1996). At mid-gestation, GAP-43 immunoreactivity is moderately intense in many fiber tracts originating from the brainstem or traveling through the brainstem, except for the corticospinal tract, where it continues to show a higher level of GAP-43 expression (Kinney et al. 1993). From mid-gestation to birth, GAP-43 immunostaining rapidly declines, so that GAP-43 expression is virtually absent in all fiber tracts in or from the brainstem, except the corticospinal tract and central tegmental tract (Kinney et al. 1993).

Similar to the spinal cord, the myelination of the brainstem is first initiated in the sensory tracts, followed by the motor tracts (Barkovich et al. 1988; McArdle et al. 1987). Histological studies show that some parts of the brainstem are well myelinated at birth, including the medial lemniscus, inferior and superior cerebellar peduncles (Brody et al. 1987; Kinney et al. 1988; Yakovlev and Lecours, 1967). As early as 10 GW, MBP expression is present in the midline of the brainstem (Weidenheim et al. 1993). According to Tanaka et al. (1995), MBP expression is first observed in medial longitudinal fasciculus of the brainstem at 20 GW and mature myelin in this area can be identified at 34 GW. The reports by Larroche (1977) and Langworthy (1933) also showed that the myelogenesis in the descending tracts from the brainstem such as vestibulospinal tract and rubrospinal tract is well underway by 24 and 32 GW, respectively.

In contrast, the myelination of the reticular formation follows a much protracted course, extending well into the 1st decade of life (Brody et al. 1987; Kinney et al. 1988; Yakovlev and Lecours, 1967). The central tegmental tract, which contains descending fibers from the cortex to the reticular formation and from the red nucleus to the inferior olivary nucleus (Afifi and Bergman, 1998; Nolte, 1993), is also hardly myelinated at birth. Specifically, less than 50% of the studied infants show mature myelin in the central tegmental tract before 144 weeks postconception age (Brody et al. 1987, Kinney et al. 1988). Reticular formation contains many structures, including those related to the control of locomotion (e.g. medial reticular formation) (reviewed in Armstrong, 1986; Whelan, 1996). Maturation of different regions of the reticular formation was not addressed in the above-mentioned histological studies. Therefore, the extent to which the locomotor-related areas of the reticular formation are myelinated at birth remains unknown. The cortico-pontine tract and the middle cerebellar peduncle, which relay activities from the cerebrum to the cerebellum, are also myelinated later when compared to the inferior and superior cerebellar peduncles (Brody et al. 1987; Kinney et al. 1988; Larroche, 1977). They are not fully myelinated until at least 1st postnatal year (Yakovlev and Lecours, 1967).

Other studies used radiological techniques such as magnetic resonance imaging (MRI) to examine the myelination process of the brainstem. At birth, most of the fiber tracts in the brainstem are well myelinated including the medial longitudinal fasciculus, medial lemniscus, inferior and superior cerebellar peduncles (Barkovich et al. 1988; Dietriech et al. 1988; McArdle et al. 1987; Sie et al. 1997). Consistent with the histological findings, the middle cerebellar peduncle does not acquire an adult appearance on T2-weighted images until 18 months (Barkovich et al. 1988). The activity level of the brainstem was also investigated by using 2-Deoxy-2[^{18}F]fluoro-D-glucose positron emission tomography (^{18}FDG PET). The local glucose utilization is the highest in the older part of the cerebellum and brain stem at 5 weeks of age, which corresponds well with the predominantly subcortical function level at this young age (Chugani and Phelps, 1986).

Based on the above evidence, some parts of the brainstem are quite mature at term, except the reticular formation, the central tegmental tract and the tracts that integrate activities from the cerebrum to the cerebellum (i.e. cortico-pontine tract and the middle cerebellar peduncle). The maturation of brainstem plays an important role in the reflexive functions during the perinatal period, which are important for the survival of the newborn (Dambska and Kuchna, 1996; Sarnat, 1989). Given the relative immaturity of tracts originating from the cortex to the brainstem (i.e. central tegmental tract, cortico-pontine tract) before the age of 1, it is reasonable to assume that the brainstem is not subject to full cerebral control at this age.

1.8.6 Maturation of the cerebrum

The cerebrum is almost devoid of myelin at birth (Larroche, 1977). Myelination of the cerebrum begins from the region around the central sulcus and proceeds outward to the poles. The posterior sites (i.e. occipital lobe) myelinate earlier than the anterior fronto-temporal sites (Kinney et al. 1988). Specifically, less than 50% of the infants show mature myelin in the frontal and temporal pole before 119 weeks and 122 weeks postconception age, respectively. The myelogenesis of corpus callosum rostrum, a structure important in relaying information between the two hemispheres, also continues well into the 2nd post-natal year (Brody et al. 1987; Kinney et al. 1988). In measuring cholesterol concentration to indicate the degree of myelination, Dobbing and Sands (1973) showed that myelination in the forebrain continued into the 3rd or 4th postnatal year.

Radiological findings also indicate that the cerebrum is far from mature before the age of 1 year in humans. ^{18}FDG positron emission tomography shows that the glucose utilization in the sensorimotor cortex continues to increase until approximately 1 year, when a pattern resembling that of an adult is seen (Chugani and Phelps, 1986). MRI studies also support the idea that the cerebrum is very immature at birth. An adult pattern of gray-white matter differentiation is not established in normal infants until 10-31 months of age (Dietrich et al. 1988). Barkovich et al. (1988) showed that the subcortical white matter matures much later than the brainstem. For example, the myelination process begins in the frontal region at 11-14 postnatal months (Barkovich et al. 1988) and is not complete until at least 3 years of age (Holland et al. 1986). Similarly, the intensity of the white matter in the corpus callosum also does not attain an adult appearance until 3 years of age (Holland et al. 1986). In summary, the radiological findings agree well with the histological data, despite slight difference in the exact timing (Barkovich et al. 1988). They all lend support to the idea that the cerebrum is generally very immature at birth. Myelination of many structures barely commences at birth and continues well into the second decade of life.

1.8.7 Maturation of the corticospinal tract

The corticospinal tract is a major motor pathway originating from the cerebrum to affect the operation of the spinal neural networks. The corticospinal tract reaches the lumbar spinal cord at about 29 GW (Sidman and Rakic, 1982). While the spinal cord and some parts of the brainstem are quite mature at term, evidence shows that the corticospinal tract is far from mature under the age of 1 in the human infant.

Histological studies show that descending pathways from the cortex have barely started myelination at birth (Langworthy, 1933; Larroche, 1977). Yakovlev and Lecours (1967) showed that the pyramidal tract starts myelination at birth and is not fully myelinated until about 2 years of age. Only 50% of infants attain mature myelin in the corticospinal tract at the level of midbrain, pons and lumbar spinal cord at approximately 50, 60 and 140 postconception weeks, respectively (Brody et al. 1987; Kinney et al. 1988).

MRI studies have also been conducted to examine the maturity of the corticospinal tract. According to T2-weighted images, the corticospinal tract at the level of internal capsule is not completely myelinated until approximately 10 months of age (Barkovich et al. 1988). Martin et al. (1988) found that only 50% of infants attain mature myelin at the level of internal capsule by 82 weeks postconception age. Holland et al. (1986) also found that the white matter tracts including the internal capsule are not well defined until 1.5 postnatal years. Taken together, the radiological findings support the idea that while the spinal cord and some parts of the brainstem are well myelinated at birth, the corticospinal tract follows a protracted course of myelination, well into the 2nd postnatal year.

Studies of reflex behavior in human infants also indicate that the spinal circuitry of human infants is not subject to full cortical control. In the newborn, the Babinski reflex is characterized by dorsiflexion of the big toe and fanning of the other toes (Ghez, 1991). It is replaced by plantarflexion of the great toe at about 18 months of age. Interestingly, patients with damage to the motor cortex also demonstrate such a reflex (Ghez, 1991; O'Sullivan, 2001), indicating that the Babinski response depends upon the integrity of the corticospinal tract and that its presence in normal infants indicates the immaturity of the tract.

In newborns, a stretch to a muscle often causes monosynaptic EMG responses not only in the stretched muscle, but also in antagonistic and other neighboring muscles (Mykleburst et al. 1986; Mykleburst, 1990; Mykleburst and Gottlieb, 1993; O'Sullivan et al. 1991). This phenomenon, known as irradiation, is most prominent at birth and is decreased over 2-4 years of age (O'Sullivan et al. 1991). Interestingly, children with cerebral palsy or adult patients with upper motor neuron disorders also show reflex irradiation (Leonard and Hirschfield, 1995; Mykleburst, 1990). The reflex irradiation in the newborns is thought to be caused by the immature descending inhibitory control from the cortex (Mayer and Mosser, 1969, 1973; Vecchierini-Blineau and Guiheneuc, 1981).

Other researchers studied the cutaneous reflexes elicited by electrically stimulating the digital nerves of fingers or toes (Crum and Stephens, 1982; Evans et al. 1990; Issler and Stephens, 1981, 1983; Jenner and Stephens, 1982; Rowlandson and Stephens, 1985a, b). Stimulation of digital nerves evoked synchronous EMG responses in neighboring muscles (i.e. reflex irradiation), which was not observed in healthy adult subjects, but was present in patients with upper motor neuron lesion (Issler and Stephens, 1983). In normal adults, the cutaneous reflex response consisted of a short-latency increase in muscle activity (E1) and later followed by a longer-latency increase (E2) (Evans et al. 1990; Issler and Stephens, 1983; Jenner and Stephens, 1982). In normal human infants, the E1 response was exaggerated and the E2 response was typically absent (Crum and Stephens, 1982; Evans et al. 1990; Issler and Stephens, 1983). With increasing age, however, the E1 component was reduced in size and the E2 component began to increase in size until an adult pattern was established during the second decade of life (Evans et al. 1990; Issler and Stephens, 1983; Rowlandson and Stephens, 1985a). Patients with damage to the motor cortex did not show the long latency excitatory component of the reflex (Choa and Stephens, 1982; Jenner and Stephens, 1982; Issler and Stephens, 1981; Rowlandson and Stephens, 1985b), just as in the infants. It was suggested that the longer latency component of the reflex is mediated by transcortical pathways. The absence of E2 component in both healthy infants and patients with damage to motor cortex indicates that the function of the corticospinal tract is immature in infants (Issler and Stephens, 1983).

Results from studies using transcranial magnetic stimulation of the motor cortex also demonstrate that the function of the corticospinal tract is far from mature. For children under 2 years of age, the threshold stimulus intensity to induce motor responses after magnetic stimulation of the motor cortex is very high [sometimes up to 100% of maximal intensity (2 tesla)]. The threshold then falls progressively until the age of 10-15 (Eyre et al. 1991; Muller et al, 1991; Nezu et al. 1997). In an earlier study, no reliable motor evoked potential (MEP) was obtained in normal children before 1.5 years of age for upper limb muscles and 4-5 years of age for lower limb muscles despite the use of maximal stimulus intensity (Muller et al. 1991). Isometric contraction of the muscle was often required to facilitate the MEP for children under the age of 8 (Koh and Eyre, 1988). In later studies, however, MEPs were successfully evoked in upper extremity muscles in neonates as young as 26 weeks of postconception age (Eyre et al. 2000, 2001). The discrepancies in results between these studies may be due to the fact that the tested muscles are relaxed in the early study (Muller et al. 1991) whereas they are contracted in the later studies (Eyre et al. 2000, 2001). Nevertheless, the thresholds for MEPs are much higher in the neonate than in the adult (Eyre et al. 2000). In addition, the conduction velocity of the corticospinal tract is much slower in neonates. For example, the maximum conduction velocities of the corticospinal tract to one of the finger muscles were estimated to be only between 10 and 30 m/s at birth, which were significantly slower than those in adults (56-85m/s) (Koh and Eyre, 1988). A progressive increase in conduction velocity occurred until around 10-15 years of age (Koh and Eyre, 1988; Muller et al. 1991; Nezu et al. 1997). These studies indicate that the maturation of the corticospinal tract follows a protracted time course.

1.8.8 Summary

Based on the above evidence, it is clear that the central nervous system development follows a caudal to rostral order of maturation in humans, just as in other animals (Martin et al. 1982; Okado and Oppenheim, 1985; Ten Donkelaar and Boer-van Huizen de, 1982). In particular, the corticospinal tract is far from mature under the age of 1 in the human infant. Therefore, it is reasonable to assume that the brainstem and spinal cord locomotor circuitry is not subject to full cerebral control in human infants from birth to the age of one year. Thus, the human infant provides a good human model to study how sensory input affects the behavior of the spinal and brainstem circuitry for stepping. In this thesis, all the experiments were conducted using human infants as subjects. Investigating the responses to specific sensory input during human infant stepping may shed light on the similarities and differences between humans and other mammals in the way the subcortical circuitry controls walking.

1.9 Summary of Objectives

In previous sections of this introduction, several important topics regarding the sensory control of locomotion have been reviewed, including the flexibility of the CPG, gating of sensory information and adaptation to transient and sustained changes in sensory inputs. Ample animal experiments have provided us with important insight into the operation of the locomotor CPG. However, more research is required to investigate how the human locomotor networks are organized. One way to approach this subject is to examine how sensory information influences the locomotor pattern. In this thesis, human infants were used to study how different types of sensory inputs affect the stepping response, thereby allowing us to gain more insight into the behavior of the human locomotor neural circuitry.

As previously discussed, hip extension and reduced load are important sensory inputs to signal the stance to swing transition in reduced preparations of the cat (Duysens and Pearson, 1980; Grillner and Rossignol, 1978). Chapter 2 of this thesis concerns whether these same factors are also involved in regulating the same transition in human infants.

Previous animal work also suggests that despite the application of various forms of disturbances, the swing phase is often not initiated until after the contralateral limb has re-established ground support, thereby maintaining equilibrium (Gorassini et al. 1994; Grillner and Rossignol, 1978). I postulated that the same holds true for human infants. This idea was investigated in Chapter 3, which describes data on the interlimb coordination in human infant stepping. Different types of perturbations to either initiate or prolong the swing phase were applied to one side. It was examined whether bilateral and functionally appropriate responses are induced to preserve equilibrium.

Although hip extension and reduced load are important inputs to control the stance to swing transition in forward walking, whether the same inputs are important in controlling the same transition in other directions of walking is largely unknown. The hip position at swing phase initiation is very different in other directions of walking. For example, in backward walking, the hip is flexed when the swing phase is initiated. There must be re-organization of the processing of sensory input to allow for different directions of walking. I hypothesized that the most powerful input to initiate the swing phase changes with the direction of walking (i.e. gating of sensory input). This hypothesis was tested in Chapter 4.

In chapter 5, we studied how human infants adapt to more sustained changes in sensory input. A mechanical tap was applied to the dorsum of the foot during early swing phase. Normally, a high step was induced (i.e.

stumbling corrective response). After such stimulation for a few consecutive steps, we observed whether the infants retained the high stepping (i.e. after-effects) following removal of the stimuli.

Overall, this thesis is devoted to studying the sensory control of walking in human infants. This thesis highlights the similarities and differences between the reduced preparations of the cat and human infants regarding the response to various types of sensory input during walking. Moreover, the results shed light on the organization of the sensory input to the locomotor CPG in humans.

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CHAPTER 2 - THE INITIATION OF THE SWING PHASE IN HUMAN INFANT STEPPING: IMPORTANCE OF HIP POSITION AND LEG LOADING

2.1 Introduction

The spinal cord in the cat contains circuitry (central pattern generator) capable of generating alternating flexion and extension activity for stereotypical limb movements such as walking (reviewed in Grillner, 1981). This circuitry can operate without any supraspinal input (Grillner, 1973) or peripheral sensory feedback (Grillner and Zangger, 1974, 1984). Evidence is mounting for a spinal central pattern generator in humans (e.g., Calancie et al. 1994; Dimitrijevic et al. 1998). Moreover, there is ample evidence that the timing and the amplitude of the motor output from the spinal generator are greatly affected by a variety of peripheral sensory information (Rossignol, 1996). The sophisticated sensory control mechanism of locomotion contributes to the activation of muscles (Severin, 1970; Yang et al. 1991; Hiebert and Pearson, 1999, Sinkjaer et al. 2000), and allows the animal to respond to changes in the external environment (Forssberg et al. 1980). One particularly well studied aspect of the sensory control of walking is the control of the transition from the stance to the swing phase.

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Grillner and Rossignol (1978) found that preventing the hip from attaining an extended position in chronic spinal cats inhibits the generation of the flexor burst and hence the onset of swing phase. It was thus suggested that the hip position is important in initiating the stance to swing transition. Evidence consistent with this hypothesis was found in decerebrate cats, where the flexor burst was promoted and the extensor activity was shortened by stimulating Ia afferents in the iliopsoas muscle using stretch and vibration (Hiebert et al. 1996). Furthermore, the initiation of the fictive locomotor rhythm in spinal cats was reported to be easier when the legs were extended (Pearson and Rossignol, 1991). Entrainment of the locomotor rhythm was also obtained by using sinusoidal stretch of the iliopsoas muscle in non-immobilized decerebrate cats (Hiebert et al. 1996) or using rhythmic hip movements in immobilized spinal (Andersson et al. 1978; Andersson and Grillner, 1981; Andersson and Grillner, 1983) and decerebrate cats (Kriellaars et al. 1994).

Apart from hip position, unloading of the extensor muscles in the limb may also be an important sensory signal involved in initiating the stance to swing transition. Duysens and Pearson (1980) found that a contraction force of more than 40N in ankle extensors led to tonic activation of the extensors in that limb. Previous animal work showed that stimulation of muscle nerves at a strength that recruits the Ib afferents in the extensors during the extensor burst causes prolongation of extensor activity. This result was found in different preparations of the cat, including immobilized decerebrate (Gossard et al. 1994; McCrea et al. 1995), non-immobilized decerebrate (Whelan et al. 1995), immobilized spinal (Conway et al. 1987; Pearson and Collins, 1993; Gossard et al. 1994; McCrea et al. 1995) and non-immobilized spinal (Pearson et al. 1992; Pearson and Collins, 1993). Furthermore, mechanical loading of the extensors in walking decerebrate cats also produced similar effects (Hiebert and Pearson, 1999). It has been proposed that the decrease in positive feedback signals carried by the group Ib afferents from the extensors at the end of stance phase allows for the subsequent generation of flexor activity.

In contrast to the robust effects of hip position and load on walking in the cat, the effects in humans are less certain. The effects of hip position in human walking have not been studied. Loading, whether by electrical (Stephens and Yang, 1996) or mechanical (Stephens and Yang, 1999; Misiaszek et al. 2000) methods, produced weak effects in adult human subjects. It is possible that there is a fundamental difference between humans and cats in the way stance and swing phase are regulated. Alternatively, it is also possible that the differences result from a difference between the state of the animal (i.e. healthy adult humans and decerebrate or spinal cats). There is some evidence to suggest that these effects are strongest in paralyzed, spinal cats (Conway et al. 1987; Pearson and Collins, 1993; Gossard et al. 1994; McCrea et al. 1995) and weaker in the less reduced preparations (Whelan et al. 1995; Whelan and Pearson, 1997; Hiebert and Pearson, 1999). Perhaps these effects are a characteristic of the spinal circuitry, which is modified by the presence of supraspinal input (Whelan and Pearson ,1997; Hiebert and Pearson, 1999).

The stepping response in human infants is thought to be mainly controlled by the brainstem and spinal circuitry (Peiper, 1963; Forssberg, 1985). Full myelination of the corticospinal tract does not occur until the age of 2 (Yakovlev and Lecours, 1967). Moreover, the threshold for eliciting muscle activity in the upper and lower extremities using transcranial magnetic stimulation is very high in children under the age of 2 (Koh and Eyre 1988; Eyre et al. 1991; Muller et al. 1991). Hence, it is reasonable to suggest that the brainstem and spinal circuitry involved in the stepping response in infants is subject to less cortical influence than in adults. Therefore, infants provide a good human model for studying the underlying behavior of brainstem and spinal circuitry in response to the changes in sensory input.

While the earlier studies have focused on the effect of either hip position or load, the relationship between the two factors is largely unknown. Hip position and load usually vary together such that the observed effects are difficult to attribute to one or the other factor. Thus, it is critical that the experiment be designed in such a way that would allow for separating the effects of hip position from those of load. Moreover, it is important to determine how different sensory inputs are combined to reach decisions for motor output.

The present study examined how hip position and load affected the initiation of the swing phase in infant stepping. Our hypothesis is that the hip position and the amount of load both play a role in regulating the stance to swing transition in infant stepping. We used a variety of hip disturbances that also allowed us to study the interaction between the change in hip position and loading. The results suggest that both hip position and load have powerful effects on modifying the step cycle in human infants. The two factors are combined to determine the stance to swing transition. The behavior of the brainstem and spinal circuitry involved in the stepping response is strikingly similar to that in reduced preparations of the cat.

2.2 Methods

2.2.1 Subjects

The infants in this study were recruited through the maternity wards of the hospitals and the public health division of Capital Health in Edmonton, Alberta. All of the infants in this study were born at term. Ethical approval for this study was obtained through the Health Research Ethics Board, University of Alberta and the Capital Health Authority, Edmonton, Alberta. Twenty-two infants aged from 5 to 12 months (average: 7.5 months) were studied. None of the infants studied could walk unassisted at the time of the experiment. Approximately 2-3 weeks before the scheduled experimental session, the parent was asked whether the infant showed any stepping response. Only those infants who made six consecutive steps, as reported by the parent, were brought in for the experiment. The parent was instructed to practice stepping with the infants for 1-2 minutes daily until the date of the experiment (Yang et al. 1998a). Informed and written consent was obtained from the parent before the infant participated in the study. The study was performed according to the Declaration of Helsinki.

2.2.2 Recording procedures

The skin was cleaned with alcohol swabs before applying the Beckman-type surface electromyographic (EMG) electrodes (bipolar 1 cm diameter, electrode separation of 1 cm). For 10 of the 22 subjects, the electrodes were placed over four muscle groups in the right leg: (1) tibialis anterior (TA), (2) gastrocnemius-soleus (GS), (3) quadriceps (Q), and (4) hamstrings (HAMS). For the other 12 subjects, the four pairs of EMG electrodes were placed on the TA and GS on both legs.

A twin-axis electrogoniometer (Penny and Giles, Biometrics, Blackwood Gwent, UK) was placed over the right hip joint to assess the hip position during disturbed and undisturbed stepping. One arm of the goniometer was in line with the mid-axillary line of the trunk and the other with the longitudinal axis of the right femur pointing toward the lateral epicondyle. A video camera (PV-950; Panasonic, Secaucus, NJ, USA) recorded the movement of the left side of the infant. In order to identify the key landmarks on video, adhesive skin markers were placed over the superior border of the iliac spine, the greater trochanter, the knee joint line and the lateral malleolus of the left leg.

A Gaitway treadmill system (Kistler Instrument Corp., Amherst, NY, USA) was used for each experiment. Two force plates located beneath the treadmill belt one in front of the other were used to measure vertical ground reaction forces during walking. Each subject was weighed by sitting the infant on one of the force plates.

To elicit walking, a researcher held the infant under the arms, with one hand on each side of the infant's upper trunk. The researcher attempted to hold the infant in a stationary position over the treadmill without imposing any movements on the infant. The infant was allowed to support as much as possible of its own weight and was centered on the treadmill at the junction of the two force plates. An accurate measurement of load on the limb at swing initiation during undisturbed stepping can be obtained by examining the rear force plate signals (for details regarding the interpretation of the force plate signals, see Fig. 2-1). The speed of the treadmill was adjusted so that optimal stepping responses could be obtained. Several trials of treadmill walking were conducted for each infant. The entire experiment was videotaped. Electromyography, force plate and electrogoniometer signals were amplified and recorded on VHS tape with a pulse code modulation encoder (A.R. Vetter, Rebersburg, PA, USA). The video and analog signals were synchronized by a digital counter at a rate of 1 Hz. The experiment was approximately one hour long for each infant.

2.2.3 Hip disturbances

Four types of disturbances were employed to study the effects of hip position and load on the initiation of swing: (1) *backward disturbance*, which extends the hip and decreases the load, (2) *mid-disturbance*, which keeps the hip in a slightly flexed or neutral position and the load remains high, (3) *forward disturbance*, which flexes the hip and decreases the load and (4) *loading*, which increases the load as the hip extends in the late stance phase. The four disturbances generated different combinations of hip position and load, so that the relationship between the two factors could be examined by comparing the responses to different disturbances. All the disturbances were applied after good, sustained stepping was obtained.

The first three types of disturbances altered the foot position on the treadmill by placing a piece of cardboard under the right foot. Because the cardboard can slide against the treadmill belt, the position of the foot, and hence the whole leg, could be manipulated by pulling on the cardboard. The cardboard was always removed immediately after the disturbance, and undisturbed stepping continued.

1. *Backward disturbance* (Fig. 2-2A). Typically, the cardboard was placed on the treadmill during the swing phase on the right. At the end

of the swing phase, the right foot came into contact with the cardboard. At this time or slightly later, one of the experimenters disturbed the limb by pulling on the cardboard in a backward direction faster than the speed of the treadmill belt. This accelerated the limb towards hip extension and also decreased the load.

2. *Mid-disturbance* (Fig. 2-2B). As the right foot stepped onto the cardboard, the experimenter maintained the right limb in a mid-stance position. As a result, the hip joint was slightly flexed or neutral and the load was relatively high during the disturbance. The disturbance was longer, because we wished to determine whether stepping could be prevented on one side while the other side continued stepping.
3. *Forward disturbance* (Fig. 2-2C). The experimenter drew the cardboard slightly forward in order to flex the hip. As the hip was being flexed, the load on the limb was decreased simultaneously because of the forward movement.
4. *Loading* (Fig. 2-2D). As the right limb approached late stance, extra load was added to the limb by briefly applying manual pressure downward on the superior iliac crest of the pelvis. Effort was made so that no observable hip flexion occurred as result of the disturbance.

2.2.4. Data analysis

The data were analyzed off-line. The EMG data were high pass filtered at 10 Hz, full-wave rectified, and low pass filtered at 30 Hz. The force plate and the electrogoniometer signals were also low pass filtered at 30 Hz. All the signals were then analog-to-digitally converted at 250 Hz (Axoscope 7, Foster City, CA, USA).

The video record was reviewed in detail to identify good sequences of walking and successful disturbances. The corresponding analog data were then identified. Sustained, undisturbed stepping was defined as four consecutive and alternating steps. All the undisturbed steps for each subject were selected and averaged using a custom written software program. The front and rear force plate signals during the averaged step cycle were then summed at each point in time, and the mean value over the cycle determined. This gave an estimate of how much weight the infant was bearing during stepping.

The disturbance was included in the analysis only if (1) it was preceded and followed by a good step, (2) it succeeded in disturbing the limb as described under "hip disturbances". The step cycle and swing durations of the undisturbed and disturbed steps were estimated by the time of right foot contact and toe off, respectively, as indicated by the force plate signals or the video image, whichever gave the clearest definition of the step cycle. The hip angle at which swing was initiated was determined by the goniometer reading, where it showed a clear reversal in direction from extension to flexion.

All disturbances were induced by the experimenter manually, so variability between disturbances was inevitable. It was therefore important to quantify the characteristics of each disturbance as accurately as possible. The magnitude of the disturbance in which the foot was displaced was determined by the distance the foot traveled during the disturbance, measured from the video record. The duration of the disturbance was also estimated from the video record (inter-frame interval: 33ms), so that the velocity of the disturbance could be determined.

In order to estimate how much load was added during the loading trials, the rear force plate signal for the right leg during the pre-disturbed and disturbed step was analyzed. An example of such a disturbance is shown in Fig. 2-8A. We assumed that the right leg slid onto the rear force plate at approximately the same time in its step cycle during the pre- and disturbed step. This is a reasonable assumption because the infants were held stationary over the treadmill while they stepped. The rear force plate signal for the right leg during the pre-disturbed step (demarcated by the vertical solid lines in Fig. 2-8A) was superimposed on that during the disturbed step (demarcated by the dashed lines), with alignment at the beginning. The difference between the two signals was obtained for each point in time, and its mean value computed. This provided an estimate of the load added by the experimenter during the disturbed step. Only those trials in which the infant was centered on the treadmill with good force plate signals were used for this analysis.

For mid-disturbances, the load of the disturbed limb was registered by the front force plate. However, its signal might be affected by the left foot because it continued to step and made contact with the front force plate as well. Therefore, the load during the disturbance was estimated by averaging the selected sections of front force plate signal when the left limb was not in contact with the front force plate. The average hip angle during the mid-disturbance was estimated by averaging the goniometer signal for the entire duration of the disturbance. These means were calculated using custom written software programs (MATLAB SIMULINK, Natick, MA, USA).

2.2.5 Statistical analysis

For each subject, the mean values of the stance, swing and step cycle duration, the hip angle (for pre-disturbed, disturbed and post-disturbed steps) as well as the load at swing initiation (for pre-disturbed and disturbed steps) were obtained by averaging the values obtained in all successful trials. The means from each subject were then entered into the following statistical tests. Repeated measures of analysis of variances (ANOVA) were used to determine if there were significant differences in (1) stance phase, (2) swing phase and (3) step cycle duration as well as (4) hip angle at swing initiation for the pre-disturbed, disturbed and post-disturbed steps (significance level at p=0.05). Student's t test with Bonferroni's correction was used to compare the data post hoc. A significance level of 0.017 was used to reduce the probability of making type I errors associated with multiple comparisons (Glass and Hopkins, 1996). Paired t tests were used for comparison of data pairs such as load and hip angle at swing initiation, magnitude and velocity of the disturbance. An alpha level was set at 0.05 for all paired t tests.

2.3 Results

The speed of the treadmill ranged from 0.23 meter per second (m/s) to 0.41 m/s (average: 0.29 m/s). The average amount of weight borne by the infants during stepping was 37 N [standard deviation (S.D.) = 16 N] or 40% (S.D. = 12%) of their own body weight (BW) (range = 15N - 85 N or 20% - 71% BW).

2.3.1 Reponses to backward disturbances

The number of successful disturbances was 28 from 10 subjects (number of trials per subject: median, 2; mean, 3). A representative example is shown in Fig. 2-3A. With the application of a backward disturbance, the load on the disturbed limb was decreased (see Fig. 2-3A, arrow on rear force plate signal) while the hip was being extended (right hip angle). The stance phase and step cycle durations of the disturbed step were shortened. The EMG recording also showed an early onset of TA burst indicating an early onset of swing.

In examining the group data, the mean hip angle at which the disturbance was initiated and ended was 21° (S.D. = 14°) and –14° (S.D. = 10°), respectively, with positive angles representing flexion. The mean displacement and velocity of the foot was -0.35 meter (m) (S.D. = 0.08 m) and -0.86 m/s (S.D. = 0.25 m/s), respectively, with positive values representing forward motion. The stance and step cycle durations for the disturbed step were significantly decreased (37% and 14%, respectively) when compared to those of the pre-disturbed step (Fig. 2-3B). The swing phase, however, showed no significant difference. The hip angle at swing initiation was similar for the pre-disturbed [-10°, standard error of the mean (S.E.M.) = 4°], disturbed (-12°, S.E.M. = 3°) and post-disturbed step (-6°, S.E.M. = 4°) and the difference was not statistically significant (not shown). With the application of backward disturbances, the load on the disturbed limb was also significantly reduced at the time of swing initiation (Fig. 2-3C). The results showed that the extension of hip and the reduction of load apparently created a condition favorable for swing initiation. Note that the number of the subjects included in the load comparison was less than that in other analyses, because some infants were not quite centered on the treadmill in some trials. Therefore, an accurate measure of load could not be obtained in some trials. This situation occurred occasionally in all other types of disturbances.

2.3.2 Responses to mid-disturbances

The number of successful disturbances obtained was 25 from 9 subjects (number of trials per subject: median, 2; mean, 3). The consistent response was that the disturbed step remained in stance phase while the contralateral limb continued to step. An individual example is shown in Fig. 2-4A. The limb was held in a slightly flexed position and the load was quite high (around 20 N or 25% BW). The disturbed limb stopped stepping while the contralateral limb continued to step. Correspondingly, the EMG from the right limb showed tonic GS and TA activity during the disturbance. In contrast, the EMG of the contralateral limb showed several alternating TA and GS bursts throughout. During the disturbance, the infant's right foot remained on the front force plate. Hence, the force signal remained high on the front force plate. Superimposed on the signal level from the force of the right foot were additional peaks associated with the stepping of the left foot (Fig. 2-4A).

When pooled across subjects, paired t tests revealed that the amount of hip flexion (24°, S.E.M. = 6°) and load (23N, S.E.M. = 3N) during the disturbance was significantly higher than those for the pre-disturbed step at swing initiation (5°, S.E.M. = 5°; 12N, S.E.M. = 2N) (Fig. 2-4B and 2-4C). The combination of increased hip flexion and load apparently created a condition unfavorable for swing initiation. Since the stance and step cycle duration could be indefinitely prolonged, and thus were entirely dependent on the duration of the disturbance, no statistical tests were used to compare the durations.

2.3.3 Responses to forward disturbances

The number of successful disturbances was 72 obtained from 14 subjects. The mean start and end position of the disturbance were 19° (S.D. = 18°) and 24° (S.D. = 17°) of hip flexion respectively. The mean displacement and velocity of the foot were 0.13 m (S.D. = 0.08 m) and 0.24 m/s (S.D. = 0.13 m/s) respectively. Note that forward and backward disturbances started at approximately the same hip angle. The amount of hip movement due to the forward disturbance was smaller than that for the backward disturbance. It was because both types of disturbances were initiated soon after right foot contact (i.e. when the hip was quite flexed). Therefore, forward disturbances did not produce as great a change in hip angle as backward disturbances. The net velocity of the forward disturbances would have been much higher had the speed of the treadmill (mean: 0.29 m/s) been taken into account. In other words, the change in the velocity of the foot was 0.24 m/s + 0.29 m/s = 0.53 m/s.

Following the application of forward disturbances, two very different responses were obtained. One type of response was that the swing phase was much delayed. Once the disturbance was over, the limb continued through a stance phase and swing was initiated only after the hip was well extended, just as in undisturbed steps. In the other type of response, hip flexion was initiated at a very flexed hip angle immediately following the disturbance. Therefore, the data for forward disturbances were divided into two groups (A and B) according to the response obtained and they were analyzed separately.

Responses from group A. The first type of response observed was that the disturbed limb did not initiate the swing until it reached an extended position after the application of the disturbance. As a result, the stance phase and step cycle durations of the disturbed step were substantially prolonged. This response was observed in 39 out of a total of 72 successful forward disturbances (12 out of 14 subjects; number of trials per subject: median, 2; mean, 3). One representative example is shown in Fig. 2-5A. During the disturbance, the hip was kept in a flexed position (around 30°) and load was decreased to about 7 N (8% BW). Swing did not occur until much later when the hip was extended to -4°. The EMG recording also showed a delay in onset of the TA burst.

In our group data, the average stance and step cycle durations of the disturbed step showed a significant increase (137% and 82%, respectively) in comparison to the pre-disturbed step (Fig. 2-5B). In this analysis, we compared the load at swing initiation for the pre-disturbed step with the load at the end of the disturbance. We were interested in whether the load was higher than normal at the end of the disturbance to prevent the initiation of swing. The results showed that the load on the right leg at swing initiation for the pre-disturbed step (11 N, S.E.M. = 3N) and that at the end of the forward disturbance during the disturbed step (7 N, S.E.M. = 1 N) were not significantly different (Fig. 2-5C). Even though the load was similar between the pre-disturbed and disturbed steps, swing was initiated only after the limb continued through the stance phase and again reached an extended position. The mean hip angle at swing initiation for the disturbed step was 4° (S.E.M. = 4°), which was not significantly different from that for the pre-disturbed step (-1°, S.E.M. = 3°) and the post-disturbed step (5°, S.E.M. = 5°).

Responses from group B. Another type of response observed following the forward hip disturbance was that the swing phase of the disturbed limb could be initiated even when the hip was in a flexed position, provided that the load was extremely low (< 5 N). This particular response was observed in 33 out of a total of 72 forward disturbances (11 out of 14 subjects; number of trials per subject: median and mean were both 3). A typical example is given in Fig. 2-6A. During the disturbance, the hip was flexed. Note that the load on the right limb was not well measured in the last one third of the disturbance because the left limb stepped on the front plate. The vertical thick dashed lines in Fig. 2-6A represent the time period when both feet were on the front force plate. Our best estimate of load on the right leg during this same period is represented by the thin dashed line, which is a linear interpolation between the two points in time when only the right foot was on the front force plate. After this period, the force of the left foot was registered only by the rear force plate whereas that of the right foot by the front force plate. Therefore, the load on the right limb at the end of the disturbance could be accurately measured by the front force plate after the left foot left the front force plate (see arrow), which was very low (5 N, 5% BW). The disturbed limb responded by initiating flexion at a flexed hip angle. The EMG signal also showed the TA burst immediately following the disturbance.

The pooled data indicated that the stance and step cycle durations for the pre-disturbed step were not significantly different from those for the disturbed step. The swing phase also showed no significant change (Fig. 2-6B). The mean hip angle at swing initiation for the disturbed step (18^{o}, S.E.M. = 3^{o}) was much more flexed than that for the pre-disturbed (-9^{o}, S.E.M. = 2^{o}) and the post-disturbed step (8^{o}, S.E.M. = 5^{o}) (Fig. 6C). The difference was statistically significant. The mean load at swing initiation on the right limb for the disturbed step was extremely low (2 N, S.E.M. = 1N) compared with that for the pre-disturbed step (13 N, S.E.M. = 1N) (Fig. 2-6D) and the difference was statistically significant.

In these particular trials, load was low (which favors swing initiation), and hip was flexed (which does not favor swing initiation). We wanted to determine whether the state of the contralateral limb might also affect when the ipsilateral limb initiates flexion in this situation. Interestingly, in most trials, the swing initiation occurred just before the contralateral limb made foot contact or when it was in early to mid stance phase (Fig. 2-7).

In order to determine if the two very different responses to forward disturbances (A, swing phase delayed and B, swing initiated) were a result of the difference in the amount of load reduction and not other characteristics of the disturbances, paired t tests were used to compare the disturbances. Only subjects who showed both types of responses were included in the analysis (9 subjects). The load at the end of the disturbance was statistically different between the two conditions (**A**: load = 7N, S.E.M. = 1N versus **B**: load = 2 N, S.E.M. = 1N). The hip angle at which the disturbances were initiated (**A**: 20°, S.E.M. = 5° versus **B**: 20°, S.E.M. = 5°), the extent of the disturbances (**A**: 0.12 m, S.E.M. = 0.01 m versus **B**: 0.18 m, S.E.M. = 0.04 m) and the velocity of the disturbances (**A**: 0.25 m/s, S.D. = 0.10 m/s versus **B**: 0.28 m/s, S.D. = 0.10 m/s) were not significantly different between the two conditions (paired t-tests, p = 0.05). Therefore, it was likely that the two types of responses resulted from differences in the load on the limb at the end of the disturbance, not to the other characteristics of the disturbance.

2.3.4 Responses to loading

The number of successful disturbances was 47 obtained from 13 subjects (median: 3, mean: 4). The mean load increase due to the disturbance for each subject was 10 N or 11% BW (S.E.M.= 2 N, 2% BW). Generally, the stance phase duration was prolonged and swing was delayed due to the disturbance. A representative example is illustrated in

Fig. 2-8A. The EMG recording demonstrated a delay in TA activation during the disturbed step. The group data showed that the stance and step cycle durations were increased significantly (30% and 22%, respectively) when compared to the pre-disturbed step (Fig. 2-8B). As the stance phase was prolonged, it was predicted that the hip would be brought to a more extended position by the motion of the treadmill belt before swing was initiated. Our results showed that there was a significant difference in the hip angle at swing initiation between the disturbed (-12°, S.E.M. = 3°) and post-disturbed step (-6°, S.E.M. = 2°). However, the difference between the pre-disturbed (-7°, S.E.M. = 4°) and the disturbed steps was not statistically significant. This could be related to the difficulty in recording hip angles accurately (see Discussion, Technical and methodological considerations). The results also indicated that the load at swing initiation was significantly higher for the disturbed step (19 N, S.E.M. = 3N) than that for the pre-disturbed step (10 N, S.E.M. = 1N) (Fig. 2-8C).

2.3.5 Possible interaction between hip position and loading

The above data suggest that the decision to initiate the swing phase may depend on the interaction of the two variables: load and hip position. For example, load at swing initiation for the disturbed step was the highest in loading trials (19 N) and the lowest in forward disturbances with extremely low load (2 N). In contrast, the trend for the hip angle at swing initiation for these same conditions were exactly the opposite, with the largest degrees of flexion occurring in forward disturbances with extremely low load (18°) and the largest degrees of extension occurring in the loading trials (-12°) with higher loads. Using these two sets of data, the relationship between hip position and load was plotted in Fig. 2-9A. The data were quite scattered, however, probably because the placement of the goniometer varied between infants and the weight of the infants were different. To remove some of the variability that resulted from the goniometer signal, the average hip angle at swing initiation for each subject was expressed as the difference from that in undisturbed stepping. A positive difference value indicates that the hip angle at swing initiation for the disturbed step was more flexed than that in undisturbed stepping. A negative value indicates the opposite. This value was referred to as the right hip angle difference in Fig. 2-9B. The load was also normalized and expressed as the percentage body weight of each infant. The scatter was much less and the data were fitted with a linear regression equation ($r = 0.74$).

Fig. 2-9A and B show data points obtained at the time swing phase was initiated under the two specific disturbance conditions: forward disturbance with very low load and loading. In order to determine whether the other situations also agreed with the same regression line, the data from these other conditions were superimposed on the regression line from Fig. 2-9B. The disturbances that greatly delayed swing initiation (mid-disturbance and forward disturbance with higher load) are shown by filled symbols (Fig. 2-9C) and the conditions that facilitated an earlier transition into swing (backward disturbances) are shown in open symbols. The majority of the data points unfavorable for swing initiation lie above the regression line whereas those favorable for swing initiation were located below it. Thus, we feel that the regression line is a good representation of the critical combination of the two factors required to initiate swing phase.

2.4 Discussion

The data demonstrate that the sensory control of stance to swing transition in infant stepping is strikingly similar to decerebrate (Duysens and Pearson, 1980; Hiebert et al. 1996) and spinal cats (Grillner and Rossignol, 1978). It is apparent that the attainment of hip extension and the reduction of load at the end of stance phase are both important for the initiation of the subsequent swing phase. Moreover, there is an inverse relationship between the two factors at the time of swing initiation, indicating that they are interdependent in determining the beginning of the swing phase.

2.4.1 Technical and methodological considerations

We will first address some technical issues that may have affected our results. First, there was considerable variability in the load and hip angle data (Fig. 2-9A). Variation in the load could be related to differences in body weight. Variation in the hip angle could be related to the difficulty in measuring joint angles accurately. While we attempted to position the goniometer in the same way for each infant, differences in the relative movement of skin and bone will clearly add to the variability. While the normalization removed some of the variability, the scatter was still large (Fig. 2-9B). Thus, while we are certain that both factors contribute to the initiation of swing phase and that there is a general inverse relationship between the two factors, we cannot be certain about the exact relationship (i.e. linear or non-linear).

Second, there was no direct measurement of the force produced by the extensor muscles. Only the vertical ground reaction forces were used as an indication of the load on the limb. Therefore, one cannot claim with certainty that the load measured reflects the load in the extensor muscles. In the loading trials, the load was applied along the long axis of the stance limb. Thus, the extensor muscles of that limb must have borne some of the extra load, because otherwise, the limb would have collapsed. In the forward disturbances, when the load measured by the force plate was low, presumably the ankle and knee extensors were unloaded, because both extensors were in a shortened position. The hip extensors, however, were in a stretched position, so they may have been experiencing some additional load due to the forward disturbances. Thus, while the ground reaction force cannot provide an accurate estimate of forces in the extensor muscles, it provides a reasonable estimate of the total load experienced. Load-sensitive receptors of all types, including those in muscle, bone and skin, could have contributed to the responses.

Third, we had a global measure of only the hip angle. Changes in hip angle will be associated with stretch of the muscles, joint capsule and skin around the hip. This study cannot address the role of these different afferent systems.

2.4.2 Similarities between human infants and reduced preparations of the cat

Infant stepping showed many striking similarities to reduced preparations of the cat. For example, in spinal cats, the generation of the alternating extensor and flexor bursts was inhibited and replaced by tonic extensor activity when the limb was held in a flexed position while the contralateral limb continued stepping throughout (Grillner and Rossignol, 1978). The human infants showed exactly the same response to mid-disturbances (Fig. 2-4). In spinal cats, the flexor burst was generated only when the limb reached an extended position (Grillner and Rossignol, 1978). The human infants showed a similar response to the backward disturbances (Fig. 2-3). Accelerating the limb toward extension causes an early onset of TA. The response to leg loading in human infants is also consistent with the findings in previous experiments in decerebrate and spinal cats (Conway et al. 1987; Pearson et al. 1992; Pearson and Collins, 1993; Gossard et al. 1994; McCrea et al. 1995; Whelan et al. 1995; Hiebert and Pearson, 1999). Increased load on the limb caused a prolongation of the stance phase and a delay of the onset of the swing phase.

2.4.3 Relationship between hip position and load

Our data indicate not only that both hip position and load contribute to the regulation of the stance to swing transition, but also that there is an interaction between the two factors. There is not a specific value of hip extension or load that must be reached before swing can be initiated, rather, it is a combination of the two factors (Fig. 2-9B). For example, as the load increases, the hip position required for swing initiation becomes increasingly more extended. On the other hand, as the load decreases, the critical hip angle for swing initiation becomes more flexed, i.e., the range of hip angles in which swing can be initiated is quite large. Observations consistent with this idea of interaction between the two systems were reported by Hiebert et al. (1996) based on their observations in decerebrate cats. They found that stretching the iliopsoas muscle by the same amount caused less reduction in the duration of extensor activity during quadrupedal walking than when the disturbed leg was immobilized. Perhaps when the limb was immobilized, the feedback from competing afferents was less and hence the same stretch in the iliopsoas muscle produced a greater effect (Hiebert et al. 1996).

Moreover, their unpublished data showed that electrically stimulating the nerves to the ankle extensors or stretching these muscles in an immobilized leg preparation also decreased the influence of the stretch sensitive afferents from the flexors to the central pattern generator (K. G. Pearson, personal communication).

Hiebert et al. (1996) have proposed a model of the organization of the sensory input to the central pattern generator based on their work on decerebrate cats. The model is based on the "half-centre" organization, which is an over-simplification of the real system, but a useful conceptual model for this purpose. According to their model, input from stretch-sensitive afferents from flexor muscles have an excitatory effect on the ipsilateral flexor half-centre and an inhibitory effect on the ipsilateral extensor half-centre, whereas the force-sensitive afferents from extensor muscles have an excitatory effect on the ipsilateral extensor half-centre only (Hiebert et al. 1996). According to their model, when forces are high in the extensor muscles, the flexor half-centre is inhibited as an indirect effect from the extensor half-centre (e.g., consistent with data from Gossard et al. 1994). However, the possibility of an inhibitory input from the force-sensitive afferents directly onto the ipsilateral flexor half-centre cannot be excluded. For example, if the generation of the flexor burst was dependent solely on the removal of the inhibition from the extensor half-centre, one would have expected a significant decrease in the level of extensor activity just before the swing phase is initiated. There were numerous examples in our data, such as that shown in Fig. 2-4, which showed that the eventual initiation of the TA burst was not preceded by a sudden decrease in GS activity. Therefore, we favor a model that includes the inhibitory input from the extensor force-sensitive afferents to the ipsilateral flexor half-centre (Fig. 2-10). Our data cannot address the specific afferents involved, but qualitative comparison with the model can still be made. For example, in the situation when load is high and hip flexors are stretched (i.e. loading trials), the model would predict that there are competing inputs to the flexor half centre on the ipsilateral side. Since the load is higher than normal in late stance, the flexor half-centre would receive more inhibition than usual. Consequently, a greater degree of hip extension would be necessary to generate sufficient excitation to allow swing to start. Conversely, the initiation of swing is also possible when the hip is quite flexed as long as the load is extremely low.

In the situation where sensory input from both the extensors and flexors to the central pattern generator is reduced (i.e. forward disturbance with extremely low load), what additional factors may have been important in determining when the swing phase was initiated? The data indicated that the activity of the contralateral limb may have an effect. In the majority of cases when the load was very low during forward disturbances, swing phase was initiated when the contralateral limb was either in very late swing or in early to mid-stance (Fig. 2-7), that is, when the contralateral extensor half-centre was active. Presumably, there might have been less inhibition from the contralateral flexor half-centre on the ipsilateral flexor half-centre at those times. Rarely did the initiation of the swing phase occur when the contralateral limb was in the middle of the swing phase. This is different from the spinal cat, in which the swing initiation occurred most frequently when the contralateral limb was either in mid-stance or in mid-swing (Grillner and Rossignol, 1978). It was suggested that the swing initiation during contralateral mid-swing corresponds to a gallop step. If this is so, our results suggest that the human infants, unlike the cat, rarely show in-phase stepping. It also indicates that the inhibition between the two flexor half-centers is quite strong. The relationship between the two extensor half-centers, in contrast, seems to be much less potent. One limb could remain in the stance for a prolonged period while the contralateral limb continues to step (Figure 2-4). Exactly how the contralateral limb affects the initiation of swing in the ipsilateral limb will require further study.

How do the various factors combine to reach a decision whether or not to initiate the swing phase? A variety of models have been proposed to explain how sensory signals might be used in combination for motor decisions (Bassler, 1993; Prochazka, 1996a, b). Our results do not support the model of finite state (conditional) control (Prochazka, 1996a). For example, one of the rules that has been proposed for this situation is that IF extensor force low AND hip extended, THEN initiate swing (Prochazka, 1996a). This rule is inconsistent with our results during forward disturbances (i.e. when the hip was flexed). Our interaction model (Fig. 2-9 and 2-10) suggests that the swing initiation in infant walking is governed by a combinatory approach similar to one used in engineering control systems, called “fuzzy logic” (Prochazka, 1996a,b). According to this model, motor behavior is determined by the relative contribution of various sensory inputs at a particular point in time. The concept of fuzzy logic is analogous to the “parliamentary principle” proposed by Bassler (1993) based on the work in stick insects. The final motor output is dependent upon the relative strength of opposing inputs. Intracellular recordings provided evidence for this parliamentary principle at the interneuronal and motoneuronal level in stick insects (Bassler, 1993). Our results suggest a similar control mechanism in regulating the initiation of swing phase in infant walking.

2.4.4 Difference between human infants and adults

There are some clear differences in the sensory control of walking between human adults and infants. The effect of changes in hip position is technically very difficult to test in adult humans. The effects of load have been tested and shown to be much more modest in adult subjects compared to infants (Stephens and Yang, 1996, 1999; Yang et al. 1998b). One of the reasons for these differences between adults and infants might be that there is increased supraspinal control of walking with maturation of the nervous system (Stephens and Yang, 1999). Presumably, cortical control can override the spinal and brainstem circuitry, and initiate the swing phase when it deems this to be appropriate. Alternatively, the spinal and brainstem circuitry might change with maturation such that these earlier patterns of control are modified. Whatever the reason, it remains interesting that the behavior of the immature human system is so similar to that in reduced preparations of the cat. Whether this spinal and brainstem circuitry plays a more important part in controlling walking after damage to the cortex or descending input remains to be determined. A decrease in hip extension during late stance is seen commonly in patients with cortical or spinal cord damage (Moseley et al. 1993; Visintin and Barbeau, 1989). Moreover, spasticity in extensor muscles may make it difficult to relax and prepare the limb for swing. There are some reports that the hip has to be moved into extension in order for spontaneous hip flexion to occur during assisted treadmill locomotion in spinal cord-injured subjects (Dobkin et al. 1995). The extensor EMG amplitude also varies with the degree of body weight support after spinal cord injury (Dobkin et al. 1995; Visintin and Barbeau, 1989). These factors could contribute to the difficulties encountered by patients in initiating the swing phase of walking and will require further study.

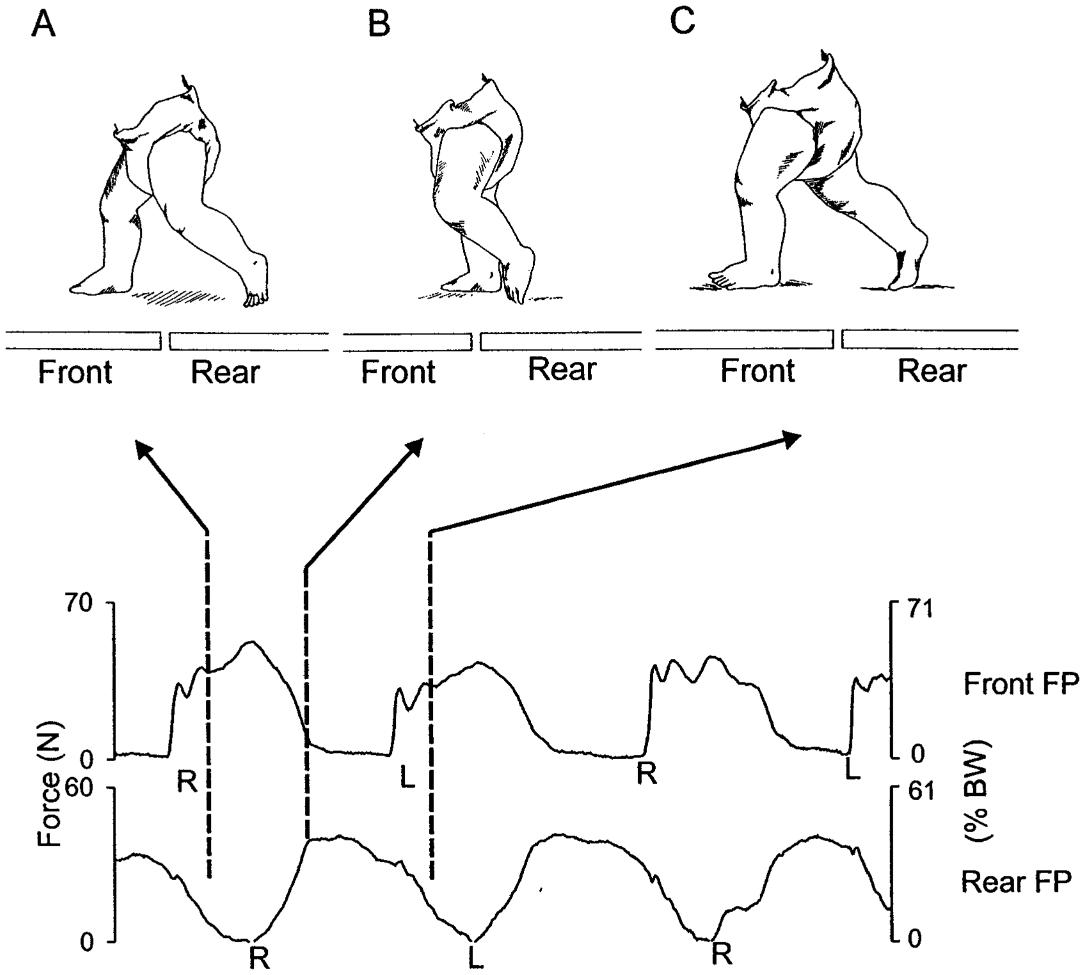

Figure 2-1. The force plate signals in relation to the step cycle

Top: Schematic illustration of the infant at three instances in the step cycle. Note that the infant was placed on the treadmill, at the junction between the front and the rear force plate. **Bottom:** The corresponding force plate signals are shown with the three instances in time indicated by the vertical dashed lines. The letters L and R under the front plate signal indicate the time of left and right foot contact, respectively. The L and R under the rear force plate indicate the time each foot slides onto the rear force plate. **A.** The right foot has made contact with the front force plate (note the corresponding rise in front force plate signal). The left leg is in late stance and its force is registered by the rear force plate (note the fall in rear force plate signal). **B.** The right leg is in the mid-stance phase. The force of the right leg is registered by the front and rear force plates (see the fall in front force plate signal and the rise in rear force plate signal). Meanwhile, the left foot is in swing phase, and does not contribute to any of the force plate signals. **C.** The right leg is in late stance and its force is registered by the rear force plate (see the fall in rear force plate signal). The left foot has made contact with the front force plate, causing a rise in the front force plate signal.

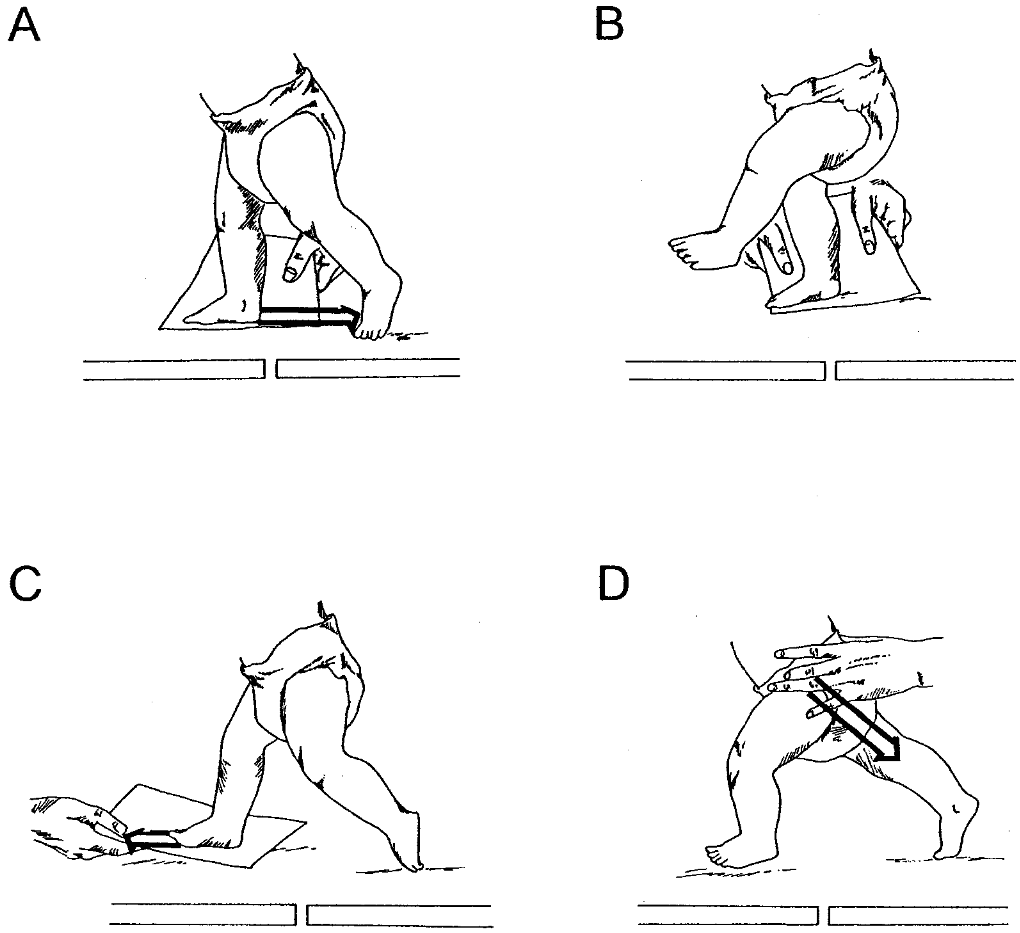

Figure 2-2. Schematic illustration of the disturbances
A. *Backward disturbance.* A piece of cardboard was placed on the treadmill during the right swing phase. Immediately after the right foot came into contact with the cardboard, the hip was pulled toward extension by drawing the cardboard backward. The load on the limb was reduced as a result. **B.** *Mid-disturbance.* The limb was maintained in a mid-stance position by keeping the cardboard stationary under the body. The load remained high. **C.** *Forward disturbance.* The hip was pulled toward flexion by drawing the cardboard forward. The load was decreased as a result. **D.** *Loading.* Extra load was added to the limb by applying manual pressure downward and backward on the superior iliac crest of the pelvis when the limb was in late stance.

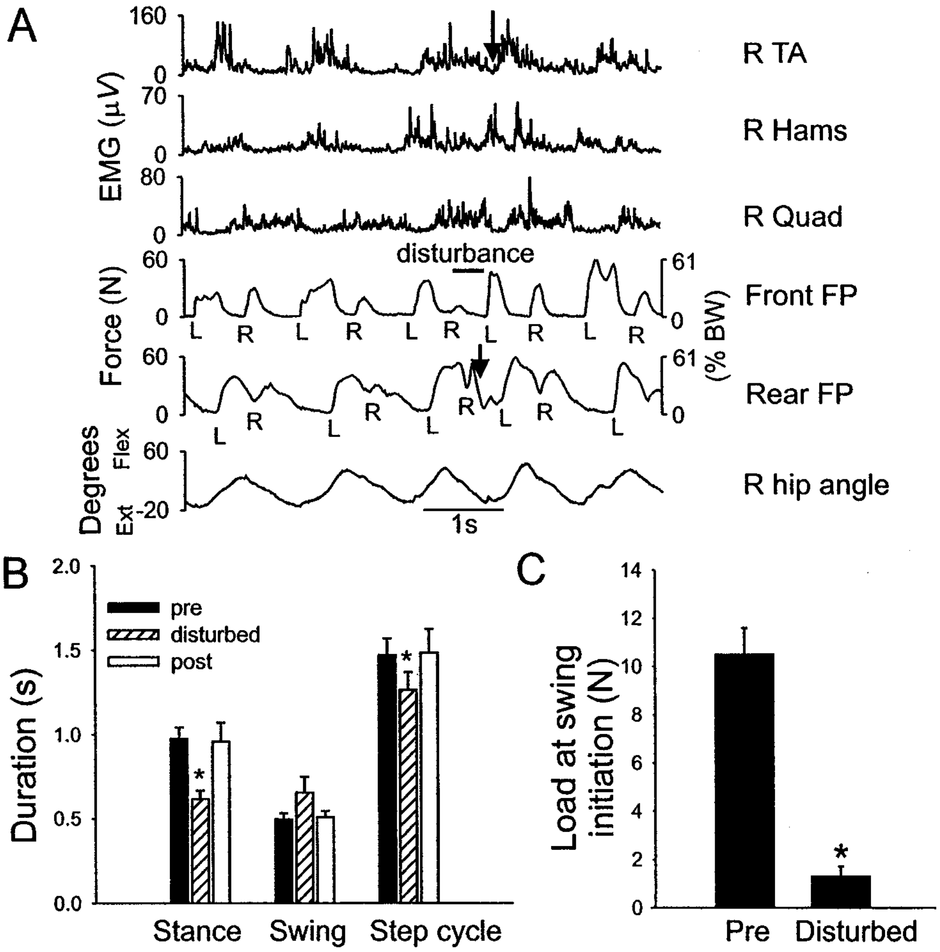

Figure 2-3. Responses to backward disturbances

A. Response to a backward disturbance from a single subject. Electromyography, force plate signals and right hip angle changes before, during and after a backward disturbance from subject GW. The duration of the disturbance is indicated by the thick horizontal line between the 3rd and 4th trace. The force in Newtons (N) and as a percentage of the infant's body weight (% BW), are both shown. Note that the rear force plate signal did not reach zero between the peaks for the steps preceding the disturbance. It is because the right foot came into contact with the rear force plate before the left foot came off. The hip was accelerated toward extension by the disturbance (see increase in downward slope of the goniometer signal during the disturbance). The load was simultaneously decreased (see arrow in rear force plate signal). The limb responded to the disturbance by initiating the swing phase earlier, thereby decreasing the stance phase and step cycle duration. Note also the early onset of TA activity caused by the disturbance (see arrow). **B.** Mean stance, swing and step cycle durations for the steps preceding (pre), during (disturbed) and after (post) the disturbance (10 subjects). The error bars represent 1 standard error of the mean. The same convention is used in all figures of the same type. * Statistically significant difference compared to the pre-disturbed step. The stance and step cycle duration were significantly shortened by the disturbance. **C.** Load at swing initiation (9 subjects). The limb was significantly unloaded by the disturbance. Some trials were excluded from the load comparison because the subject was not quite centered on the treadmill. An accurate measure of load, therefore, could not be obtained in those cases.

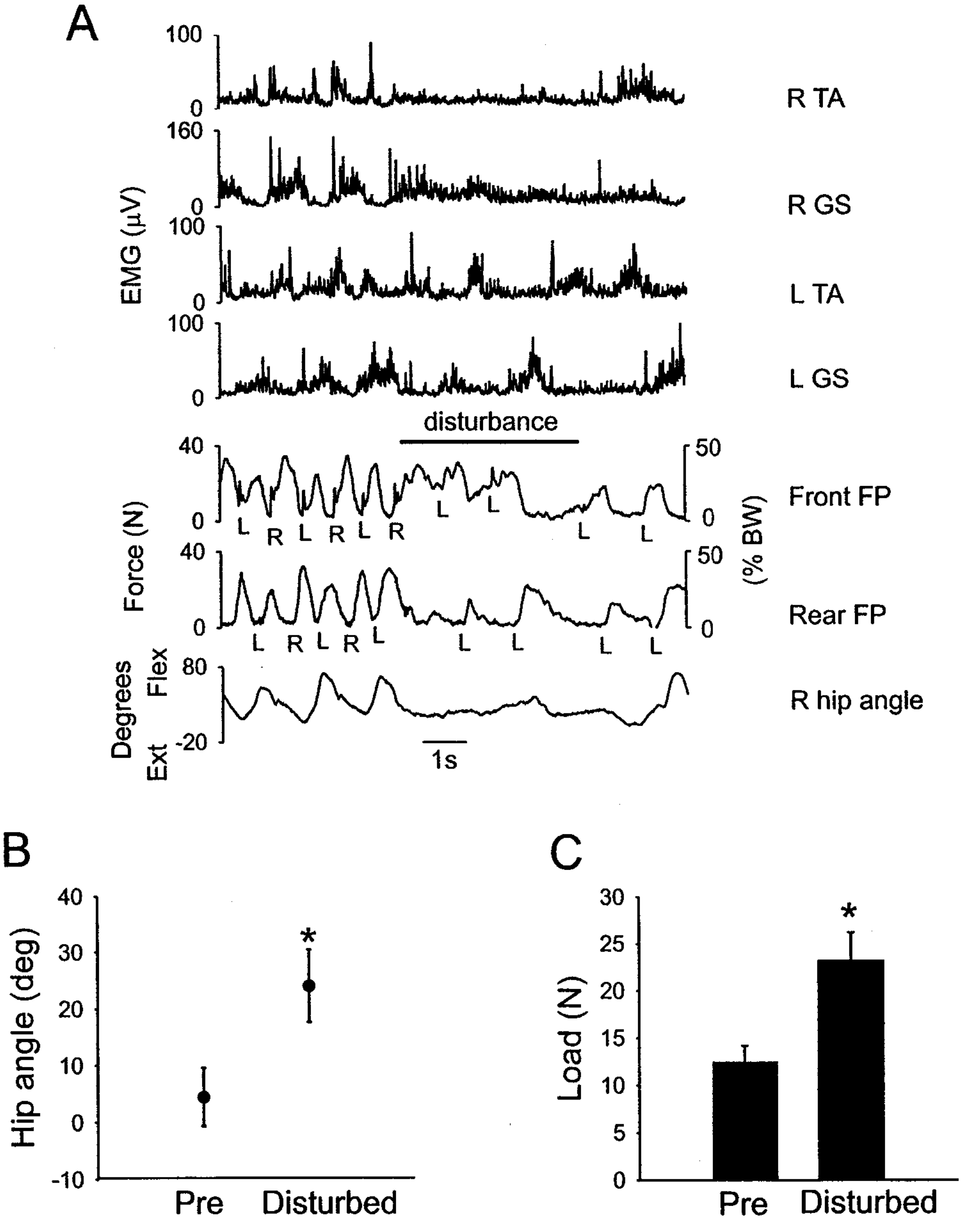

Figure 2-4. Responses to mid-disturbances

A. Responses to a mid-disturbance from a single subject. Electromyography, force plate signals and right hip angle before, during and after a mid-disturbance from subject JU. During the disturbance, the hip was kept in a slightly flexed position (10°–20°). The load of the limb remained high (about 25% BW, see front force plate signal). The right limb stopped stepping while the left limb continued to step. Note the termination of alternating TA and GS activity in the right limb during the disturbance whereas the left limb showed alternating TA and GS throughout. **B.** Mean hip angle at swing initiation for the pre-disturbed step and the hip angle during the disturbance (9 subjects). The hip angle was more flexed during the disturbance than that at swing initiation for the pre-disturbed step. **C.** Load at swing initiation for the pre-disturbed step and the load during the disturbance (9 subjects). The results show that the load remained high during the disturbance.

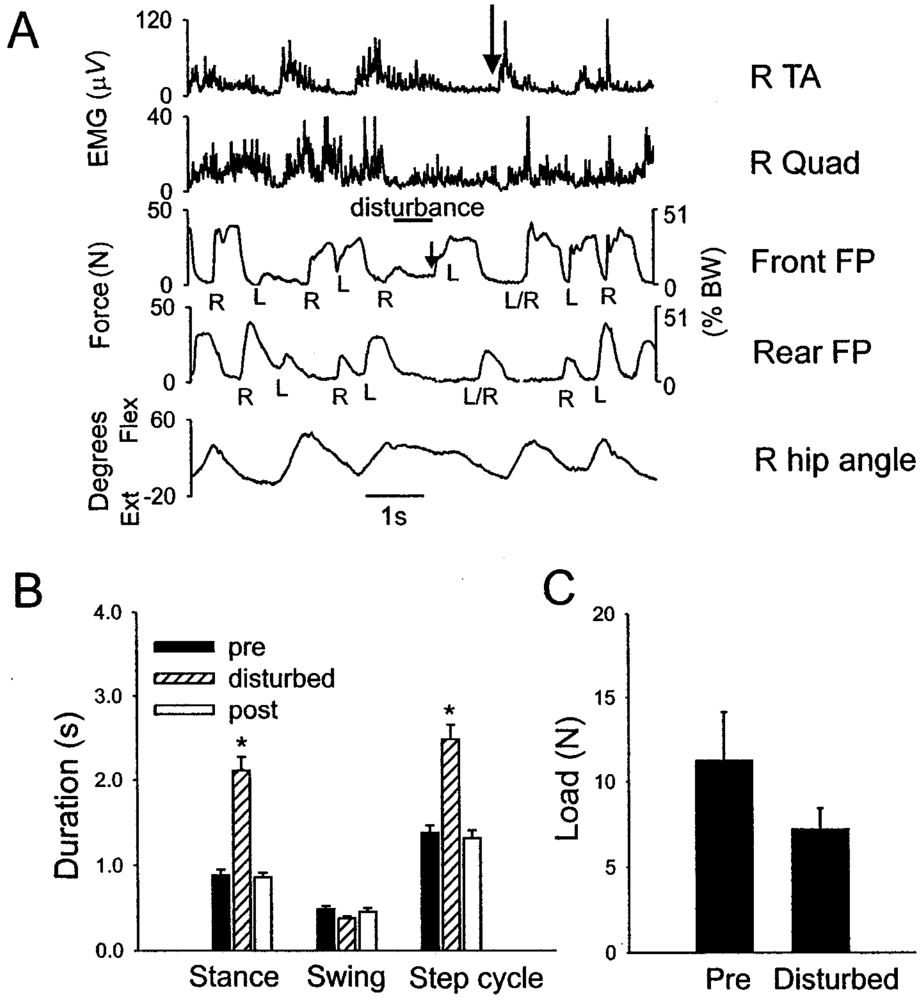

Figure 2-5. The first type of response to forward disturbances

A. Example of the first type of response (from group A) to a forward disturbance from a single subject. Electromyography, force plate signals and right hip angle before, during and after a forward disturbance from subject GW. The right hip was kept in 20°-30° in flexion transiently (see goniometer signal). The load was also reduced to 8% BW by the disturbance (see arrow in front force plate signal). Despite the reduction in load, the limb continued its stance phase after the disturbance was over (note the increase in front force plate signal immediately after the disturbance). The swing phase was initiated only when the hip was again well extended. The stance and step cycle durations were prolonged as a result. Note also the delay in TA onset (see arrow). The L/R on the rear and front force plate signals indicate that both legs moved back onto the rear force plate and then stepped onto the front force plate at approximately the same time. **B.** Mean stance, swing and step cycle durations for the steps preceding, during and after the disturbance (12 subjects). The stance and step cycle duration were significantly prolonged by the disturbance. **C.** Load at swing initiation for the pre-disturbed step and the load at the end of the disturbance (9 subjects) were not significantly different.

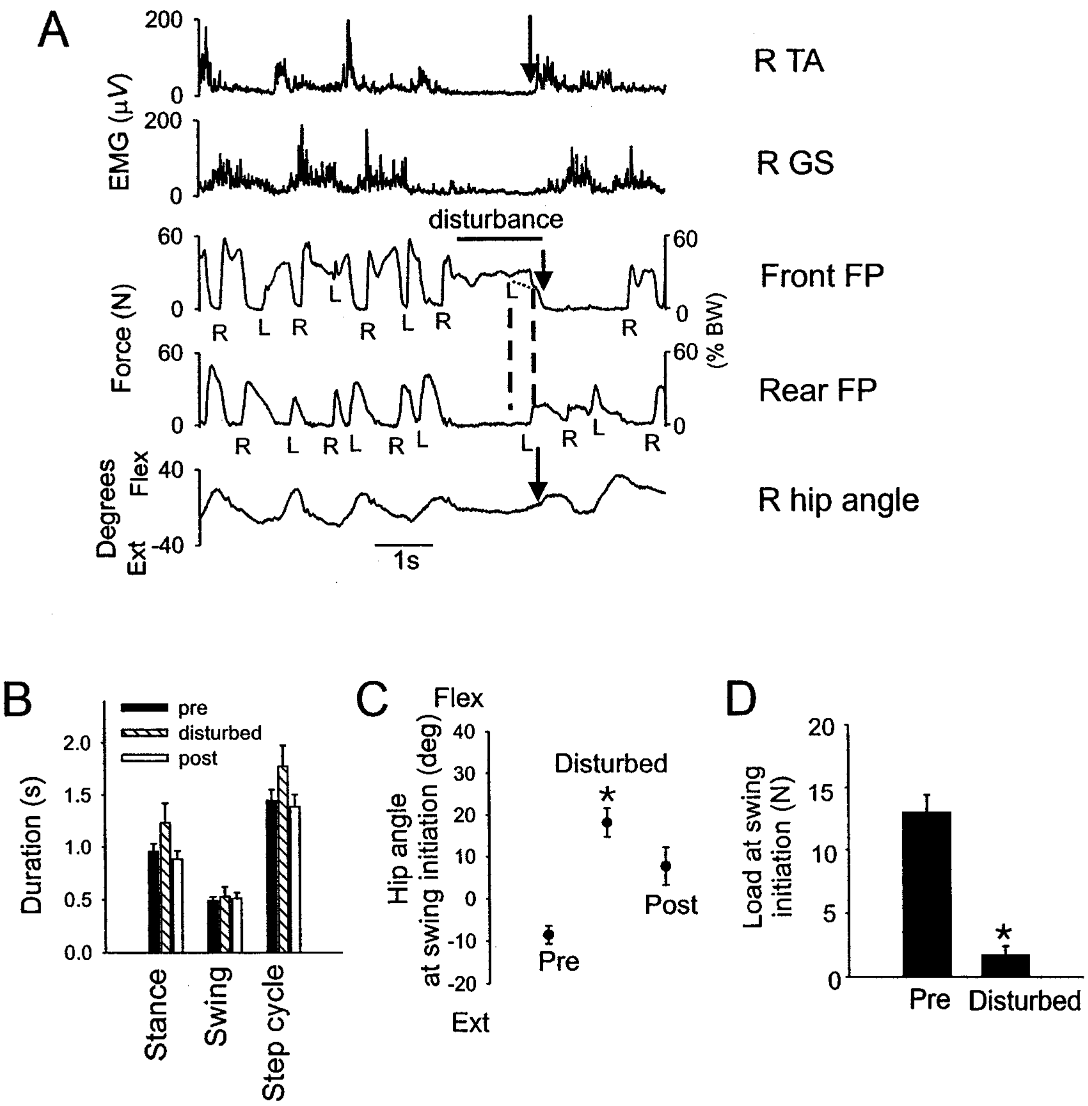

Figure 2-6. The second type of response to forward disturbances
A. Example of the second type of response (from group B) to a forward disturbance from a single subject. Electromyography, force plate signals and right hip angle before, during and after a forward disturbance with extremely low load from subject NA. The right hip was transiently flexed to about 10°. The thick dashed lines demarcate the period when both feet were on the front force plate. The thin dashed line in the front FP signal represents our best estimate of load on the right leg during this same period (see text for more details). Note that the right limb was almost completely unloaded at the end of the disturbance (5% BW, see arrow in front force plate signal immediately following the second thick dashed line). Note also the decrease in GS activity during the disturbance. The limb responded by initiating a swing phase while the hip was still in flexion (see arrow in R hip angle trace). Note the onset of TA burst associated with the initiation of swing phase (see arrow). **B.** Mean stance, swing and step cycle durations for the steps preceding, during and after the disturbance (11 subjects). The stance and the swing phase durations did not show any significant change. **C.** Right hip angle at swing initiation for the steps preceding, during and after the disturbance (11 subjects). The hip angle for the disturbed steps was much more flexed than the pre-disturbed step. **D.** Load at swing initiation for the steps preceding and during the disturbance (9 subjects). The limb was significantly unloaded by the disturbance.

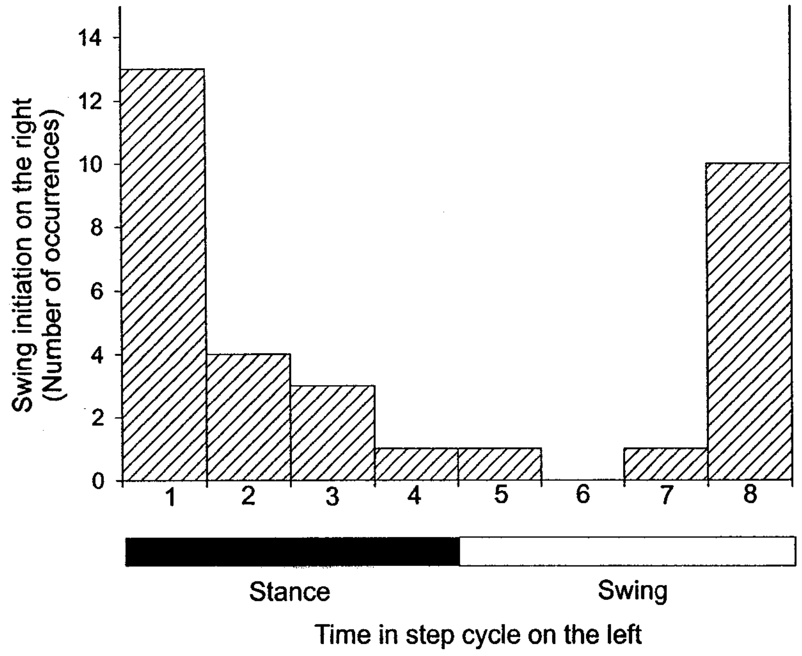

Figure 2-7. Swing initiation as a function of the state of the contralateral (left) leg

The left step cycle duration (horizontal axis) was divided into eight different bins, four for the stance phase and four for the swing phase. The first bin begins at the time of left foot-floor contract and the last bin ends at the same event. The vertical axis indicates the number of occurrences of swing initiation of the right leg following forward disturbances with extremely low load (total: 11 subjects, 33 trials). The data shows that in most trials, swing phase was initiated on the right when the contralateral limb was either in early to mid-stance phase or in very late swing (i.e. just before left foot contact).

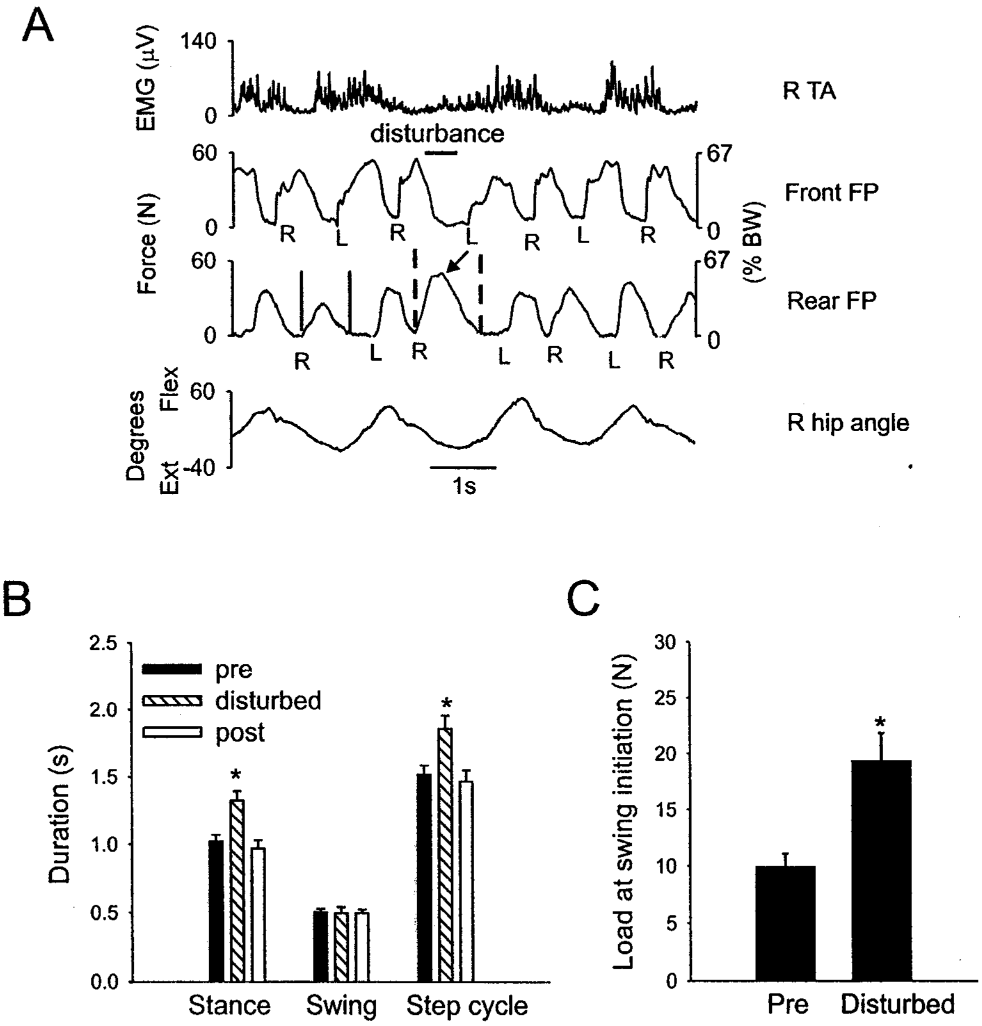

Figure 2-8. Responses to loading disturbances

A. Response to a loading disturbance from a single subject. Electromyography, force plate signals and right hip angle before, during and after a loading disturbance from subject BJ. Additional load was applied to the right limb during late stance. Note the increase in force associated with the disturbance (see arrow in rear force plate signal). The limb responded by delaying its swing initiation, thereby increasing the stance and step cycle durations. Also note the delay in TA onset. **B.** Mean stance, swing and step cycle durations for the step preceding, during and after the disturbance (13 subjects). The stance and step cycle durations were significantly prolonged due to the disturbance. **C.** Load at swing initiation for the steps preceding and during the disturbance (12 subjects). The load was significantly higher for the disturbed step than that for the pre-disturbed step.

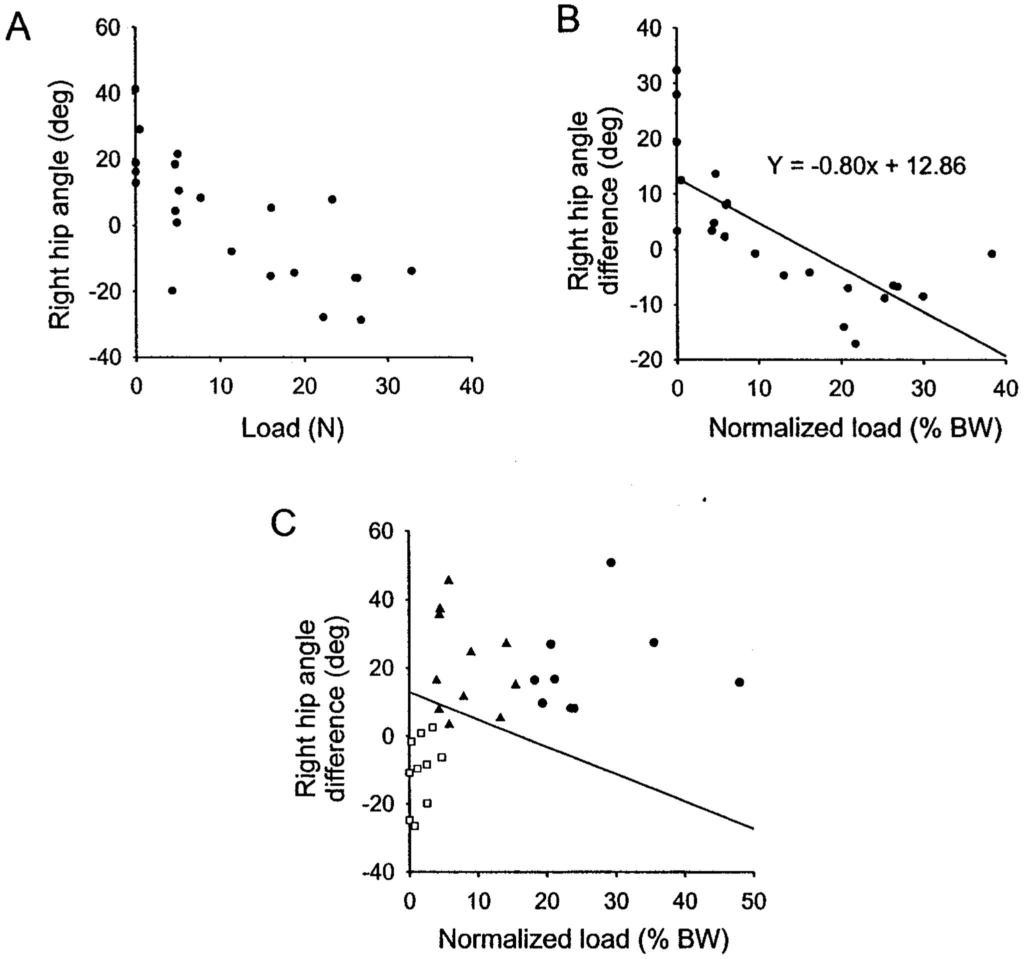

Figure 2-9. The interaction of hip position and load

A. Each data point represents the mean hip angle and load at swing initiation for each subject obtained in all successful trials of loading (12 subjects) and forward disturbances with extremely low load (9 subjects). Although a general inverse relationship was noted, the data were quite scattered. **B.** The data from part A were normalized before plotting in this graph. The hip angle at swing initiation was subtracted from the mean hip angle at swing initiation in undisturbed stepping for each subject and expressed as the right hip angle difference. The load was expressed as the percentage of each subject's body weight. The variability was much reduced. The data points were fitted with a linear regression equation (r=0.74). The results indicate that there is an inverse relationship between hip position and load in regulating the stance to swing transition. **C.** The data points for mid-disturbances (9 subjects, represented by filled circles) and forward disturbances (not including those with extremely low load) (11 subjects, represented by filled triangles) were superimposed on the regression line. These represent conditions where swing phase was not initiated. Almost all the data points are located above the line. The data points for the backward disturbances (10 subjects) are shown by open squares. These represent conditions where swing phase was initiated early. All of the data points fall below the line. Thus, the area above the line represents conditions unfavorable for swing initiation whereas that below the line represents conditions favorable for swing initiation.

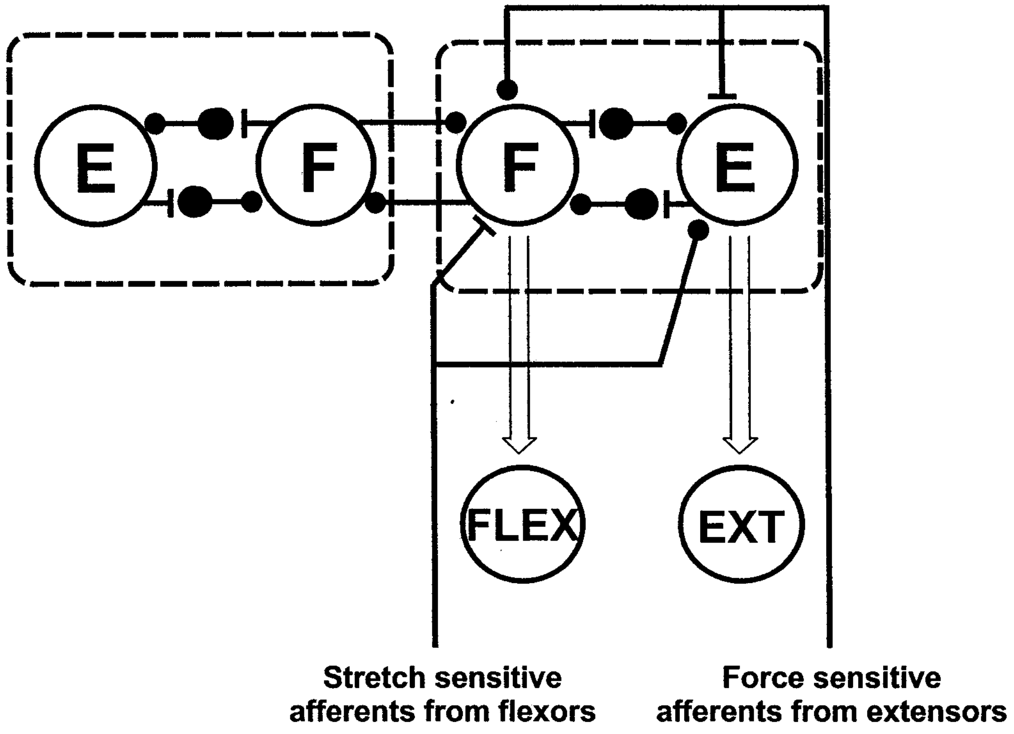

Figure 2-10. A model of the organization of the sensory input to the central pattern generator

The locomotor rhythm for each limb is generated by mutually inhibiting extensor (E) and flexor half-centers (F). The black dots represent inhibitory connections whereas the bars represent excitatory connections. The extensor and flexor half-centers on each side project to the extensor (EXT) and flexor (FLEX) motoneuronal pools respectively. The stretch-sensitive afferents from the flexors inhibit the ipsilateral extensor half-center and excite the ipsilateral flexor half-center. The force-sensitive afferents from the extensors excite the ipsilateral extensor half-center and inhibit the ipsilateral flexor half-center. Strong reciprocal inhibition exists between the two flexor half-centers.

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CHAPTER 3 - INTERLIMB CO-ORDINATION IN HUMAN INFANT STEPPING

3.1 Introduction

Precise coordination of the limbs during walking is essential for all terrestrial animals to ensure a safe base of support. This requirement is particularly critical for bipeds, who have a higher center of gravity and only two limbs to provide support. When unexpected disturbances occur during walking, adult humans respond by generating co-ordinated responses in both legs (Berger et al. 1984; Dietz et al. 1984, 1986; Eng et al. 1994; Schillings et al. 2000). For example, if one leg unexpectedly hits an obstacle early in the swing phase, co-ordinated muscle activity is elicited in both limbs. The disturbed limb is lifted over the obstacle, while the contralateral limb remains in the stance phase longer to wait for the completion of the corrective movement.

Are these responses to perturbations part of the innate ability of the circuitry that controls walking? There is some suggestion that co-ordinated responses to mechanical perturbations are not mature in the young, since perturbations similar to those used in adults elicit much greater coactivation of antagonistic muscles in children between the ages of 1 and 8 years (Berger et al. 1985). On the other hand, the co-ordination

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between the two limbs shows considerable maturity in infants. For example, when infants (7 months old) were manually held to step on a split-belt treadmill with the belts running at different speeds, they made adjustments in the movements of both limbs to maintain their alternating pattern (Thelen et al. 1987), much like adults (Dietz et al. 1994, Prokop et al. 1995). Moreover, when we supported infants to step on a treadmill, and transiently disturbed one limb during the swing phase, adjustments were seen in the contralateral limb (Yang et al. 1998b). How do the two limbs respond to unilateral disturbances during stepping in young infants?

The objective of the present study was to examine: (1) whether infants generate appropriate responses to maintain ground contact when a disturbance forces one limb to initiate the swing phase; (2) whether disturbances that lengthen the swing phase result in adjustments in the contralateral limb to maintain ground contact; and (3) whether the two limbs can perform the stance and the swing phase synchronously (i.e., in-phase).

3.2 Methods

3.2.1 Subjects

The infants in this study were recruited through the Royal Alexandra Hospital and the Public Health Division of the Capital Health Authority in Edmonton, Alberta, Canada. Ethical approval for this study was obtained through the Health Research Ethics Board, University of Alberta and the

Capital Health Authority, Edmonton. Informed and written consent was obtained from a parent before the infant participated in the study. The experiments were conducted in accordance with the Declaration of Helsinki for experiments on humans. Twenty-eight infants aged from 4 to 12 months (average: 7.8 months) were studied. All the infants were born at term. A few weeks before the scheduled experimental session, the parents were contacted by phone and instructed on how to induce stepping in infants. They were asked to attempt to elicit stepping once a day, for a few days. Only those infants who showed six or more consecutive and alternating steps, as reported by a parent, were studied. None of the infants studied were able to walk unassisted.

3.2.2. Recording Procedures

Surface bipolar Ag-AgCl electromyographic (EMG) electrodes (either Beckman-type 1 cm diameter or Kendall SOFT-E pediatric electrodes) were applied over the tibialis anterior (TA) and gastrocnemius-soleus (GS) muscles on each leg, after the skin was cleaned with alcohol swabs. A twin-axis electrogoniometer (Biometrics, Blackwood, Gwent, UK) was placed over the right hip (21 subjects) or the left hip (1 subject) or both hip joints (6 subjects). One arm of the goniometer was aligned with the mid-axillary line of the trunk and the other with the longitudinal axis of the femur. A video camera (PV-950; Panasonic, Secaucus, NJ, USA) recorded the movement of the left side of the infant. Adhesive skin markers were placed over the superior border of the iliac spine, the greater trochanter, the knee joint line and the lateral malleolus of the left leg.

A Gaitway treadmill (Kistler Instrument Corp., Amherst, USA) was used. Two force plates located beneath the treadmill belt, one in front of the other, were used to measure vertical ground reaction forces during stepping. The infant was held under the arms from behind by one of the experimenters or a parent. The infant was placed on the treadmill at the junction between the two force plates, and allowed to support as much of her/his weight as possible (i.e., without the knees flexing excessively). An attempt was made not to impose any movements on the infant, but to support them in a stationary position over the treadmill. The speed of the treadmill was adjusted to one that generated the most stepping (between 0.23 and 0.32 m/s). Typically, the length of each trial was between 1 and 2 minutes. Force plate, EMG and electrogoniometer signals were amplified and recorded on VHS tape with a pulse code modulation encoder (Vetter, Rebersburg, PA, USA). All trials were videotaped. The video and analog signals were synchronized by a custom made timer, which generated pulses at a rate of 1 Hz. The length of the experimental session for each subject was approximately 1hour.

3.2.3 Leg Disturbances

All disturbances were applied after sustained stepping (i.e., minimum of 4 alternating, consecutive steps) was obtained. Three different types of disturbances were used.

I. *Rapid extension of the right hip during stance.* In this series of experiments, we wished to study the effects of forcing the right leg into swing phase at different times of the left step cycle. A piece of cardboard was placed on the treadmill under the right foot during the right swing phase. At different times after the right foot came into contact with the cardboard (Fig. 3-1A and B), the cardboard was pulled backward rapidly to extend the hip and unload the limb, promoting a condition favorable for swing initiation. Disturbances were applied during all phases of the left step cycle. This was possible because the right limb could be held in the stance phase by holding the cardboard at a position that maintained the limb in mid-stance (Pang and Yang, 2000). Typically, the left limb would continue stepping, so that extension of the right hip could be timed to occur at different times in the left step cycle.

II. Extension of the right hip during swing. Forward motion of the swing limb was briefly interrupted by manually extending the hip during the swing phase (Fig. 3-1C). We were interested in determining whether the swing phase could be prolonged and whether any compensatory reactions took place in the left leg.

III. Disturbances to promote in-phase stepping. We wanted to determine whether the two limbs could stay in the same phase of the step cycle (i.e., stance or swing) together. A piece of cardboard was placed on the treadmill under one foot during the ipsilateral swing phase. After the foot made contact with the cardboard, the leg was kept in mid-stance while the contralateral leg continued stepping (Fig. 3-1D). When the contralateral leg reached a similar anteroposterior position to the ipsilateral leg in the stance phase (Fig. 3-1E), both legs were allowed to move backward together. We observed whether stance phase could coexist on both sides for an extended period of time, and whether the swing phase could be initiated at the same time on both sides.

3.2.4. Data analysis

The data were analyzed off-line. The EMG data were high-pass filtered at 10 Hz, full-wave rectified, and low-pass filtered at 30 Hz. The force plate and the electrogoniometer signals were low-pass filtered at 30 Hz. All the signals were then analog-to-digitally converted at 250 Hz (Axoscope 7, Axon Instruments, Foster City, CA, USA). The video record was reviewed in detail to identify all successful disturbances. Disturbances were included in the analysis only if the goniometer signal showed that the disturbance was appropriate (i.e. a sudden increase in the angular velocity of hip extension for disturbances in the stance phase, and a reversal in the direction of movement from flexion to extension for disturbances during the swing phase). For disturbances to promote in-phase stepping, the disturbance must have allowed both legs to move backward in the stance phase at the same time. All disturbances must be preceded by a minimum of 4 consecutive steps and followed by at least 1 complete step.

The effect of the disturbances on the hip was quantified from the hip goniometer signal (i.e. duration, magnitude, velocity). The stance and swing phase durations were estimated by the time of foot contact and toe off, respectively, as indicated by the force plate signals in conjunction with the video image. If the EMG signal was contaminated by artifact such that the onset and termination of the EMG bursts were difficult to identify, the trial was excluded from EMG analysis. Overall, 17% of trials were eliminated for this reason. The percentage of trials unsuitable for EMG analysis was rather large, because adipose tissue in the legs and the small size of muscles cause the signal to be very small in some infants, resulting in a poor signal to noise ratio.

The data obtained during disturbances that extended the right hip during the stance phase were separated according to the state of the left leg when the disturbance began. Five phases were distinguished in the left step cycle. (1) Early stance phase began when the left foot made contact with the treadmill and ended when skin markers on the greater trochanter and the knee joint line became vertically aligned on the video. (2) Late stance phase followed the early stance phase and ended 200ms before the onset of the left TA burst for the disturbed step. (3) Transition phase followed the late stance phase, and ended when the left foot came off the treadmill. (4) Early swing phase began when the left foot came off the treadmill and ended just before the left knee started to extend. (5) Late swing phase followed the early swing phase and ended when the left foot made contact with the treadmill.

The degree of coactivation of antagonistic muscles in response to disturbances that extended the hip during the stance phase was estimated, to facilitate comparison with an earlier study (Berger et al. 1985). The time series of the EMG from the TA and GS muscles on the disturbed (right) side were aligned in time from the beginning of the disturbance, and averaged for each subject, across all disturbances of this type. Data from disturbances applied at different times in the contralateral step cycle were pooled because there were no differences in the response on the ipsilateral side. Only those subjects who had at least three trials of disturbances were considered. Coactivation was estimated by a Pearson's product moment correlation coefficient between the averaged EMG time series for the two muscles, over a 500ms period from the onset of the disturbance.

The phase interval between the two legs was quantified for all types of disturbances. The onset of the step cycle in one leg was expressed as a function of the step cycle of the contralateral leg. In this calculation, step cycles were defined by the onset of the TA EMG activity (see illustration in

Fig. 3-4A). The vertical dotted lines in Fig. 3-4A mark the onset of the TA EMG burst in one limb for two consecutive steps. The time interval between the two lines represents the step cycle in that limb ('d'). The 'e' represents the period between the onset of the TA EMG burst in one limb and that in the contralateral limb. The phase interval (as a percentage) between the two sides was calculated as follows:

phase interval = (e/d)100.

The phase interval would be close to 50% if the two limbs showed perfect alternate stepping. In-phase stepping was arbitrarily defined as a phase interval of less than 20% or greater than 80%.

For disturbances that promoted in-phase stepping, the phase interval as well as the double support time and double swing time were quantified. Since both legs were allowed to move backward in the stance phase together in these disturbances, either limb could initiate the swing phase. The limb that initiated the swing phase first was referred to as the *leading limb* and the other limb as the *trailing limb*.

3.2.5 Statistical analysis

All statistical tests were conducted with mean values from each subject (i.e. averaged across all successful trials). Repeated measures of analysis of variance (ANOVA) was used to compare timing and phase relationships for steps preceding, during and following the disturbances at an alpha level of 0.05 for type-I errors. Bonferroni post hoc t-tests were conducted at a significance level that was corrected for the number of comparisons, in order to reduce the probability of making type I error associated with multiple comparisons (Glass and Hopkins, 1996). All results are quoted as means ± S.E.M. unless otherwise stated.

3.3 Results

3.3.1 Rapid extension of the right hip during stance

Swing phase on the right leg was almost always initiated when the left leg was in the stance phase or late swing phase (Fig. 3-2), in spite of the fact that near equal numbers of disturbances were applied at all five phases of the left step cycle (31 ± 1; mean ± S.D.). Disturbances applied at different times in the contralateral step cycle did not differ in the mean angular velocity of the hip [(112 ± 4 degrees per second (deg/s)] and the peak hip extension angle reached at the end of the disturbance (-5 ± 1 deg/s). All disturbances were followed by activation of the right TA muscle (i.e., initiation of the swing phase) at approximately the same latency [(269 ± 18 milliseconds (ms)]. There were no significant differences in this latency between disturbances applied at different times in the contralateral step cycle. Compensatory adjustments were seen on the contralateral side, so that when swing phase was initiated on the right side, the left leg was either in the stance phase or close to being in the stance phase (i.e. late swing).

When disturbances occurred during the late stance phase of the contralateral side, the duration of the contralateral stance phase was prolonged. An example is shown in Fig. 3-3A. In this trial, the right leg was held in mid-stance (see the dashed line between the 4th and 5th trace) while the left leg continued to step (see rhythmic EMG activity in left TA muscle). Rapid extension of the right hip was initiated when the left leg was in the stance phase. The left stance phase was prolonged, so that the right leg initiated its swing phase while the left leg still maintained contact with the treadmill surface. The alternating pattern of the left and right steps is most clearly seen in the black bars that illustrate the right and left stance phase (Fig. 3-3A, bottom). The pooled data demonstrated that the duration of the left stance phase for the disturbed step was significantly prolonged (Fig. 3-3B).

When disturbances occurred during the early swing phase of the contralateral side, the contralateral swing phase was truncated (Fig. 3-4A). The period between the onset of the left GS EMG activity was measured for the pre-disturbed, disturbed, and post-disturbed step (a, b and c, respectively, in Fig. 3-4A). The left GS EMG burst was initiated early in reaction to the perturbation (see slanted arrow in L GS signal), thereby shortening the left swing phase. The initiation of the right swing phase (see arrow in R TA signal) occurred soon after left foot contact. The pooled data in Fig. 3-4B showed that there was significant truncation of the left swing phase due to early onset of the left GS EMG activity.

However, the duration of the left TA EMG burst was not significantly changed.

In contrast to the above, disturbances that occurred during early stance and late swing phase of the contralateral side did not cause any significant changes in the contralateral step cycle, because this coincides with the time the right swing phase would normally be initiated (not shown).

The degree of co-contraction between GS and TA muscles in the disturbed limb was generally small. Three examples are shown in Fig. 3-5. Subject RO showed the highest level of co-contraction, whereas subjects JU and BZ showed low levels of co-contraction. The correlation coefficients were all near or below zero for 10 out of 11 infants (range: +0.05 to –0.77), indicating either no relationship between the two muscles or an inverse relationship (possibly reciprocal inhibition). Only one infant (RO) showed a high correlation coefficient, indicating either co-activation of the antagonist muscles or cross-talk between the antagonists.

3.3.2 Extension of the right hip during swing

Disturbances applied during the swing phase of the right leg caused a lengthening of both the ipsilateral swing phase and the contralateral stance phase. Fig. 3-6A shows an example from a single subject. The right TA EMG burst and the left GS EMG burst were both prolonged during the disturbed step (slanted arrows). In the pooled data (8 subjects), the duration of the right swing phase, the right TA EMG burst and the left stance phase were all significantly prolonged (Fig. 3-6B).

3.3.3 Disturbances to promote in-phase stepping

Data from a single subject are shown in Figure 3-7. The right limb was first held in a mid-stance position by preventing the cardboard from sliding back (thick line indicating disturbance). Once the left leg reached a similar position to the right leg in the stance phase, both legs moved toward extension together, as indicated by the arrows in both goniometer signals. Note also the coactivation of the GS muscles on both sides during the same time period. The subsequent swing phase was initiated by the right leg first (slanted arrow in the R TA signal) while the left leg remained in stance. The left leg then initiated its swing phase (slanted arrow in the left TA burst) after the right leg had regained contact with the treadmill surface.

The pooled data (8 subjects) showed that the stance phase could coexist on the two sides for a long period of time (773 ± 490 ms; mean ± S.D.). Typically, the rhythmic alternating activity between the two limbs was quickly re-established at the time swing phase was initiated on one side. Only 8% of the steps immediately following the disturbances were classified as in-phase. In these cases, double swing time was 72 ± 54 ms (mean ± S.D.).

To characterize the stepping behavior between the two limbs further, the phase interval for the steps surrounding disturbances applied during the stance and swing phase (i.e. type I and II disturbances) were quantified. Before the disturbance was applied, the two legs stepped alternately, with no steps classified as being in-phase (Fig. 3-8). During the disturbed step, there was still a strong tendency for the movement of the two legs to remain alternate, but more steps fell into the classification of being in-phase (20% of the steps). In the first step after the disturbance, the alternate stepping pattern was almost completely restored (6% of steps in-phase).

3.4 Discussion

The results indicate that during infant stepping, disturbances to one limb are compensated for by both limbs, so that one limb maintains ground support at all times. Moreover, the two limbs could perform the stance phase simultaneously for extended periods of time, while they rarely initiated the swing phase simultaneously. Even when stepping was disrupted by the disturbance, rhythmic alternate stepping was largely restored in the step immediately following the disturbance. Thus, coordination of leg movements during infant stepping is consistent with the requirements for independent walking, long before independent walking is possible.

3.4.1 Infants respond in a similar way to adults

The response of infants to perturbations during stepping is very similar to that observed in adults during walking. Dietz and colleagues (Berger et al. 1984; Dietz et al. 1984) have studied the response of adults to a perturbation that extends the limb in the stance phase by a rapid acceleration of the treadmill belt. This is similar to the disturbances that rapidly extended the hip in the stance phase in this study. The disturbances used by Dietz and colleagues were faster (average velocity of approximately 1.8 m/s compared with 0.86 m/s in infants), and shorter in duration (average of 70 ms in adults with 221 ms in infants). Nevertheless, the responses were qualitatively similar. When disturbances occurred during the contralateral swing phase, infants truncated the swing phase in the contralateral leg to re-establish ground contact, just as the adults. In another type of disturbance, the forward motion of the swing leg was halted briefly in adults (Dietz et al. 1986). This is similar to the swing phase disturbances used here. The durations of the disturbances used here (mean, 171 ms) were similar to the longest durations used with the adults (160 ms). Again, the reactions of the contralateral limb were qualitatively similar. The durations of the contralateral stance phase and extensor EMG burst were prolonged in infants just as in the adults. In summary, when swing phase is either initiated or prolonged by the disturbance, the compensatory response of the contralateral leg always led to maintained ground support both in adults and in infants, presumably to help prevent a fall. This is despite the fact that infants in our study could not walk independently and were supported to step, so there was no risk of falling.

It is interesting that Berger et al. (1985) reported that young children responded to accelerations of the treadmill with more coactivation of antagonistic muscles than adults, both during standing and walking. In the current study, however, a similar type of disturbance (rapid extension of the hip in the stance phase) elicited reciprocal activity in the antagonistic muscles at the ankle in most infants during the first 500ms after the disturbance (Fig. 3-5). One possible explanation for the difference between the studies is that the children in the earlier study (Berger et al. 1985) were all independent walkers (aged 1-8 years) and had to cope with disturbances to their equilibrium induced by the perturbations. In contrast, the infants studied here were supported to step and could not fall. Since co-contraction leads to stiffening of the limb, it may have been an effective way to minimize the threat to equilibrium in older children. Indeed, coactivation of antagonistic muscles during undisturbed stepping in infants has been shown to be much higher when the infants have to support more of their own weight and control their equilibrium (Okamoto and Goto, 1985). Coactivation of antagonistic muscles has also been reported for adults when certain types of disturbances threatened equilibrium during walking (Misiaszek et al. 2000). Thus, coactivation of antagonists in response to a perturbation may represent a strategy to compensate for novel perturbations to equilibrium.

3.4.2 Subtle differences in interlimb co-ordination between species

There are many similarities in the way humans and other mammals coordinate their limb movements to respond to disturbances during walking (Pang and Yang, 2000; Yang et al. 1998a,b). Moreover, we show here that in response to any disturbance that causes an initiation or prolongation of the swing phase on one side, the contralateral side initiates or prolongs its stance phase in infants. A similar pattern of response has been reported for a variety of preparations in the cat (Forssberg et al. 1977, 1979; Gorassini et al. 1994; Hiebert at al. 1996; Matsukawa et al. 1982; Schomburg et al. 1998). Thus, in general, initiation of swing phase on one side is contingent upon the contralateral limb being in the stance phase.

Some subtle differences between the species were also noted. For example, the phase interval between the left and right sides showed a broader distribution during undisturbed walking in intact cats compared with the undisturbed steps in the infants (compare English, 1979, Fig. 2 with current study, Fig. 3-8). Many steps in the cat hindlimbs show a phase interval that would be classified as in-phase in our study (i.e. $<72^o$ or $>288^o$ in their measure) during undisturbed walking, compared with 0 and 6% in-phase steps for those preceding and following a disturbance in the infants. In another study with chronic spinal cats, Grillner and Rossignol (1978) applied unilateral disturbances during walking. The disturbances were similar to the disturbances used here with infants, where the hip was rapidly extended during the stance phase. The cats initiated swing phase on the disturbed side during either the middle of the stance or the swing phase of the contralateral side (see Fig. 3A in Grillner and Rossignol, 1978). This is in contrast to infants, who initiated the swing phase only during the stance phase or late swing phase of the contralateral limb (Fig. 3-2). While the differences between species will require further study, our results suggest there are subtle differences that may be related to the requirements of bipedal versus quadrupedal walking.

3.4.3 Organization of the central pattern generator

Simultaneous initiation of the swing phase on both sides was relatively uncommon in infants (Fig. 3-8). In contrast, the two limbs could coexist in the stance phase for long periods of time. We cannot rule out the possibility that swing phase might have been elicited simultaneously on both sides more often with disturbances not tried here. Nevertheless, the results agree well with the half-center model proposed for the organization of the central pattern generator in other mammals (Brown 1911, 1914; Hiebert et al. 1996; Lundberg, 1980). In this model, the flexor half-centers (responsible for the flexion or swing phase) on each side of the body mutually inhibit each other. This is consistent with the fact that swing phase was rarely initiated at the same time on both sides in our infants. In contrast, the extensor half-centers on each side have no mutual inhibitory connections in this model, again agreeing with the easy coexistence of the stance phase on the two sides.

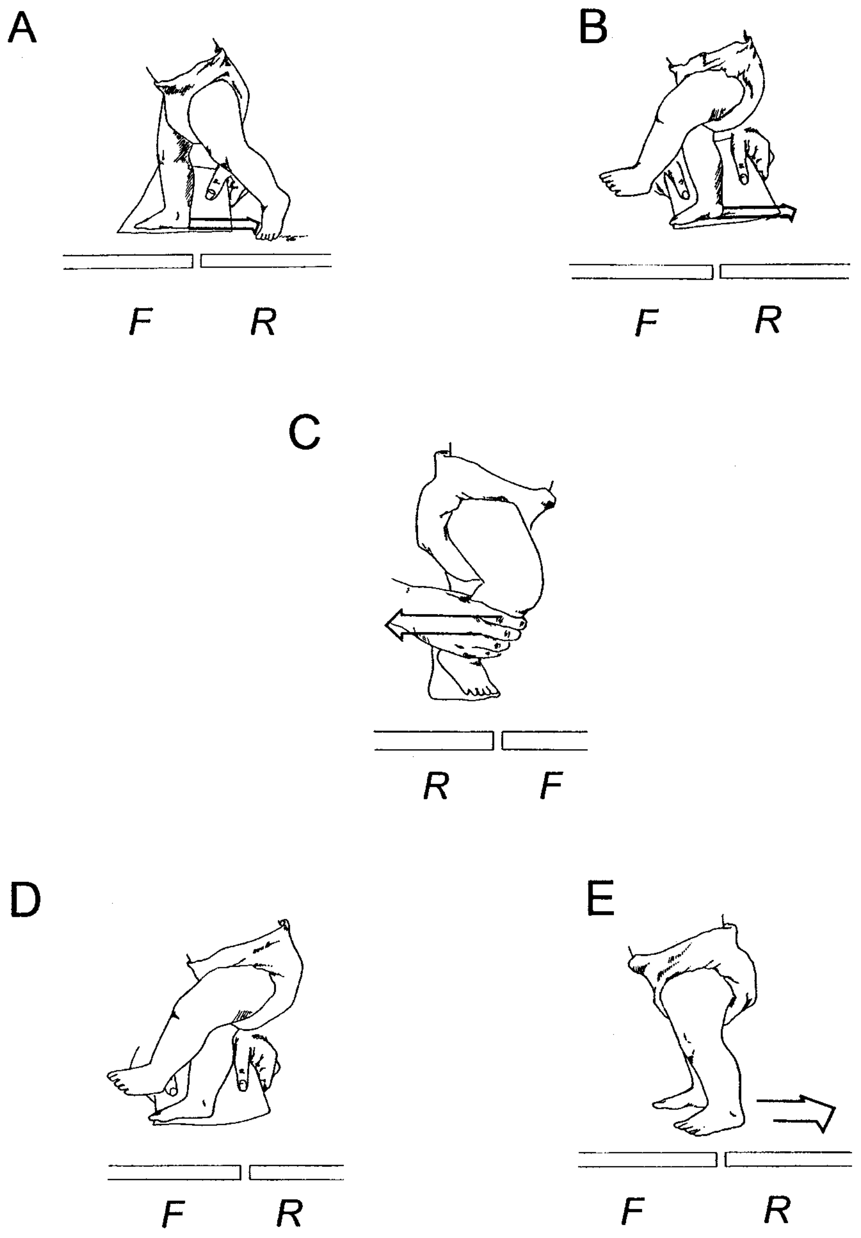


Figure 3-1. Schematic illustration of the disturbances
The infant was viewed from the left side in **A, B, D, E** and from the right side in **C**. All the disturbances were applied when the infant was walking forward on the treadmill. ***F*** and ***R*** represent front and rear force plate, respectively. Three types of disturbances were applied. **A & B.** *Rapid extension of the right hip during stance.* **A** and **B** show a disturbance during left late stance phase and late swing phase, respectively. **C.** *Extension of the right hip during swing.* The forward motion of the limb was interrupted for a short period of time manually. **D & E.** *Disturbances to promote in-phase stepping.* The right leg was held in mid-stance phase by using the cardboard **(D)**. When the left leg reached a similar position to the right leg, the two legs were allowed to move backward together with the treadmill belt **(E)**.

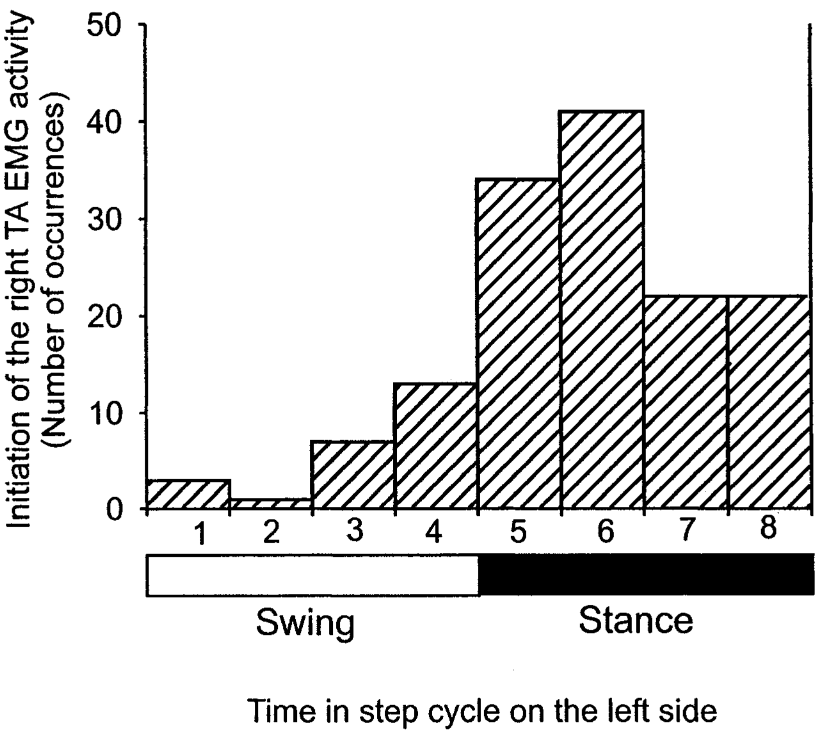
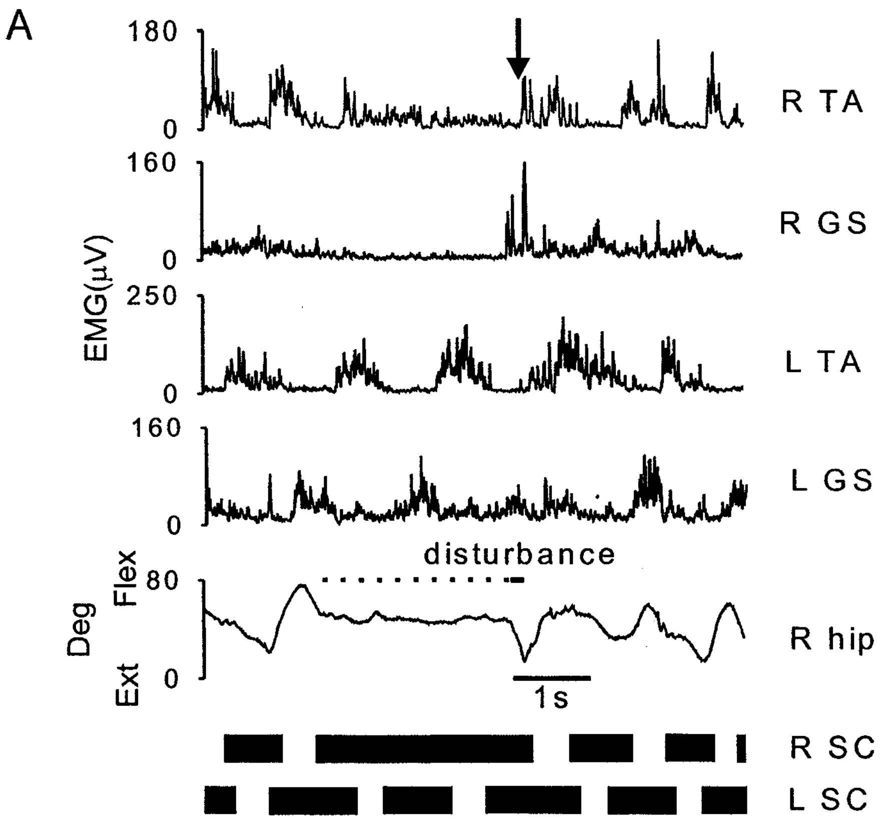


Figure 3-2. Initiation of the swing phase as a function of the contralateral step cycle

The horizontal axis represents the time in the left step cycle, which was divided into eight different bins, four for the swing phase and four for the stance phase. The first bin begins at the time of left toe off and the last bin ends at the same event. In response to rapid extension of the right hip, swing phase was most often initiated when the contralateral leg was in the stance phase or late swing phase.



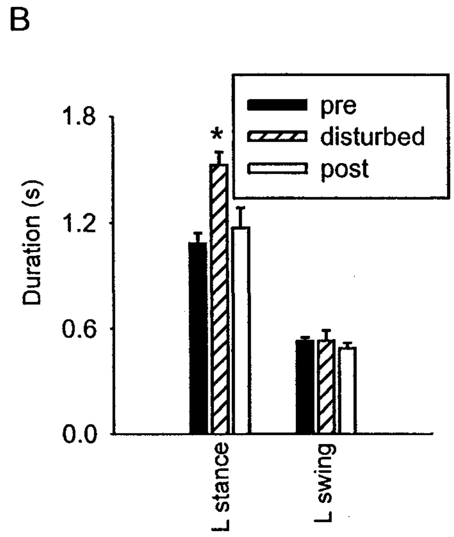
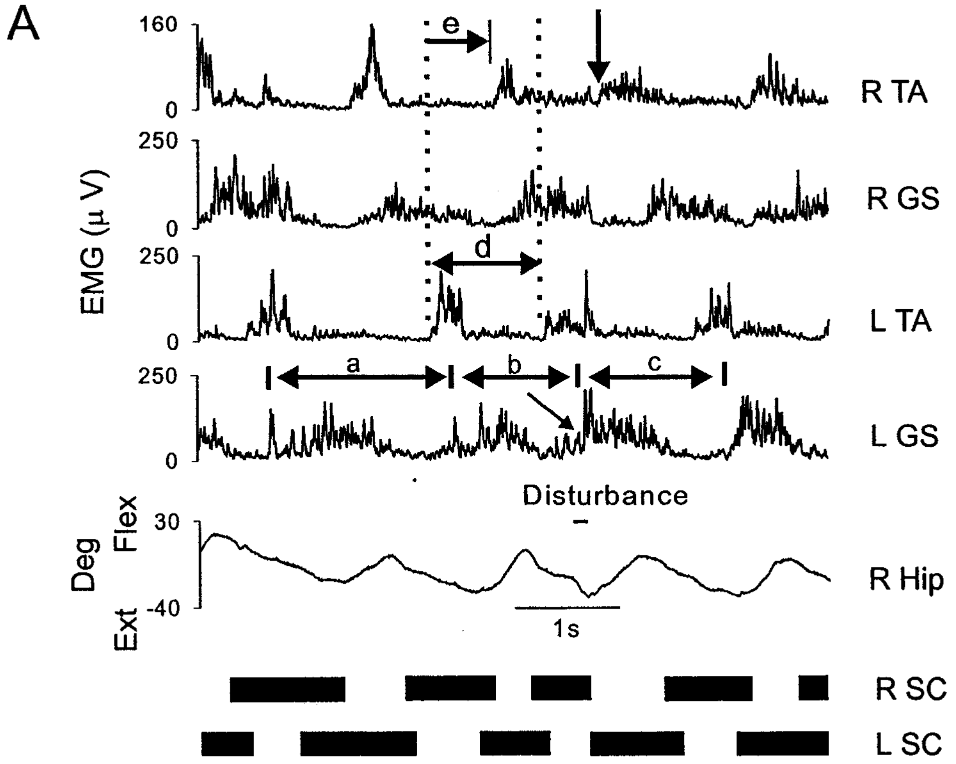


Figure 3-3. Response to rapid extension of the right hip during contralateral late stance phase

A. Response from a single subject (GW). Muscle activity from surface electromyography (EMG), right hip angle (R hip) and step cycle (SC) of both legs before, during and after the disturbance. The horizontal dashed line between the 4th and the 5th trace represents the time when the right leg was held in a mid-stance position before rapid hip extension (thick horizontal line) was applied. The black bars represent stance phase whereas the spaces between the black bars represent swing phase. The same figure convention is used in figures 3-4, 3-6 and 3-7. Swing initiation on the right side occurred when the left leg was still in stance phase (see arrow in R TA signal). **B.** Average duration of the left stance and left swing phase for the steps preceding, during and following the disturbance (pooled across data from 9 subjects). The error bars represent one standard error. * Statistically significant difference compared with the step preceding the disturbance.



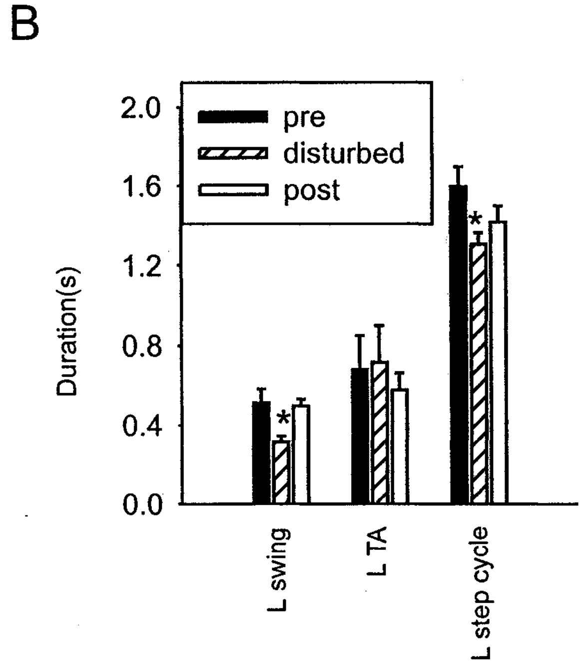


Figure 3-4. Response to rapid extension of the right hip during contralateral early swing phase

A. Responses from a single subject (BN). The disturbance caused an early onset of EMG activity in the right TA (vertical arrow) and left GS (slanted arrow), which led to a shortening in the duration of the right stance and left swing phases. The duration of the step cycle was also altered (compare pre-disturbed, disturbed and post-disturbed steps, denoted by a, b, and c respectively). **B.** Average duration of the left swing phase (11 subjects), left TA EMG burst (8 subjects), and left step cycle (9 subjects) for the pre-disturbed, disturbed, and post-disturbed steps.

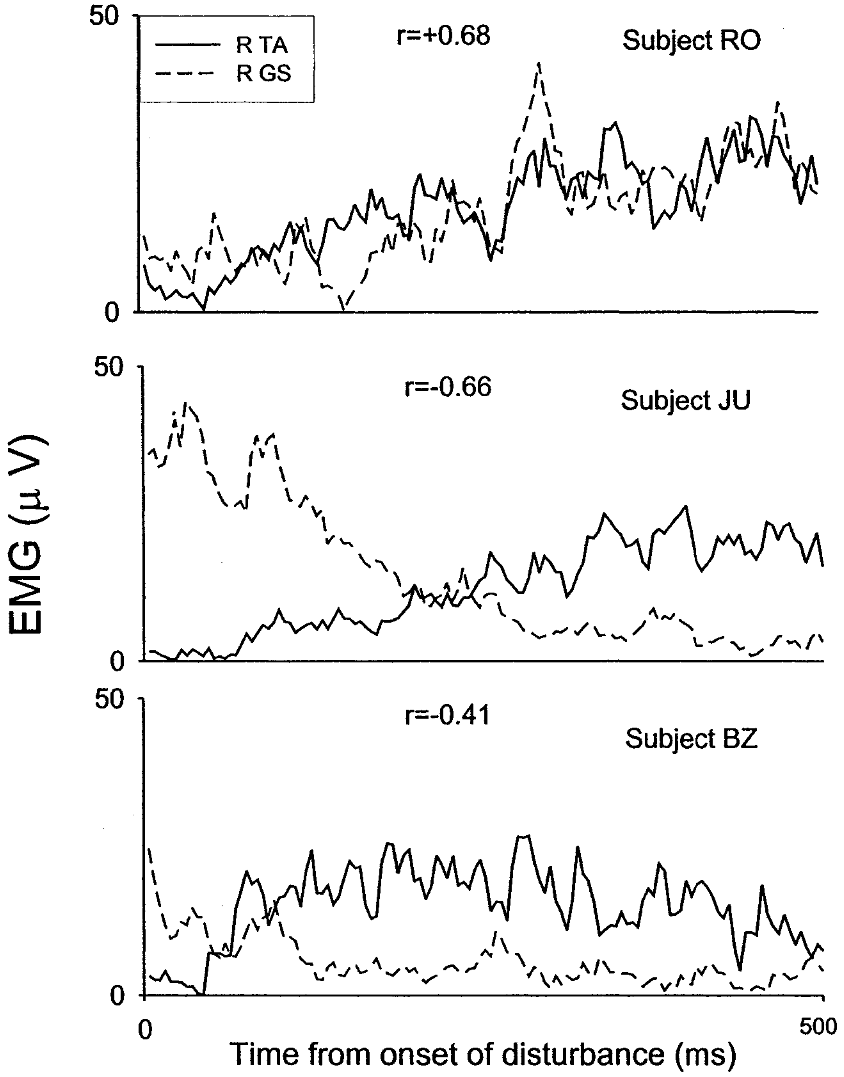


Figure 3-5. The level of co-contraction of the R TA and GS muscles following a disturbance

The level of co-contraction of the R TA and GS muscles following rapid extension of the right hip is shown for three subjects. Subject RO showed a high level of co-contraction whereas subject JU and BZ showed a low level of co-contraction. Pearson's product moment correlation coefficients (*r*) for the TA and GS EMG activity are also shown.

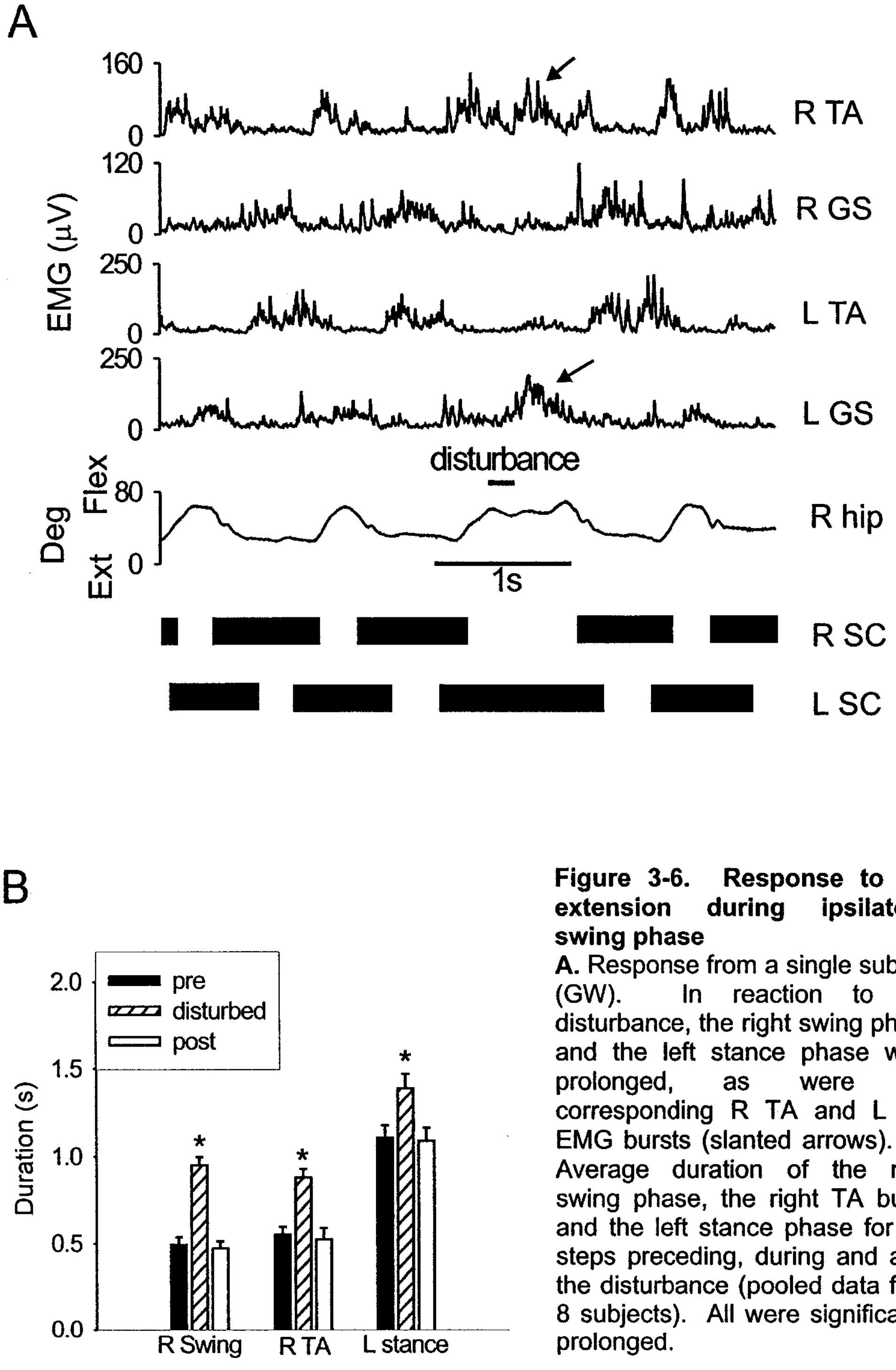


Figure 3-6. Response to hip extension during ipsilateral swing phase

A. Response from a single subject (GW). In reaction to the disturbance, the right swing phase and the left stance phase were prolonged, as were the corresponding R TA and L GS EMG bursts (slanted arrows). **B.** Average duration of the right swing phase, the right TA burst, and the left stance phase for the steps preceding, during and after the disturbance (pooled data from 8 subjects). All were significantly prolonged.

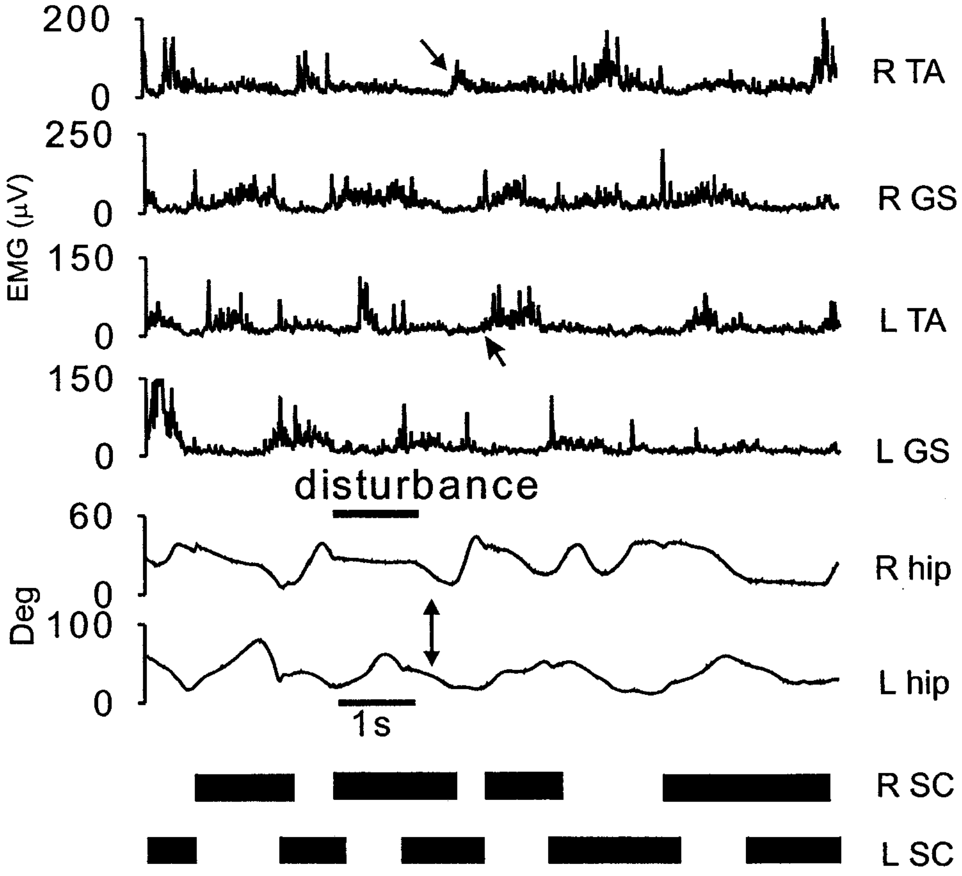


Figure 3-7. Response to disturbances that promoted in-phase stepping

Response from a single subject (RN). The right foot was held in a slightly flexed position right after it hit the treadmill surface (see right hip angle during the duration of the disturbance, positive angle represents flexion). Shortly after the left foot contacted the treadmill surface, the right leg was allowed to move backward synchronously with the left leg (vertical arrows point to simultaneous hip extension on both sides). The double limb support time was much longer in the disturbed step. The right leg initiated the swing phase first, while the left leg remained in the stance phase. Swing phase was initiated later on the left side after the right limb re-established ground support.

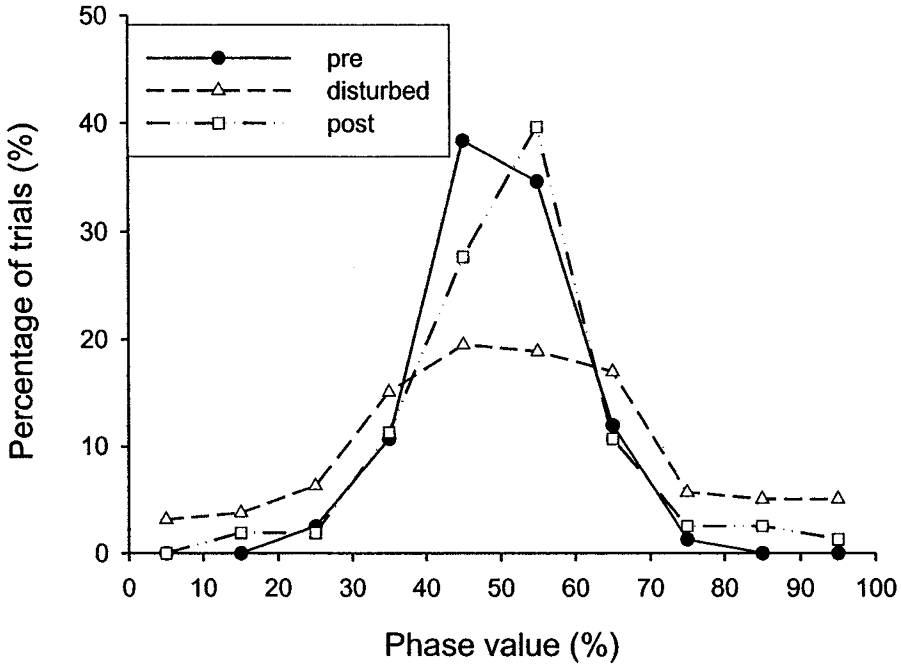


Figure 3-8. Phase interval for the steps surrounding disturbances
Distribution of phase intervals for the steps preceding, during and after the disturbances. Data obtained from disturbances applied in the stance and swing phase were pooled. Although the disturbed step showed increased in-phase stepping, a strong tendency for alternate stepping remained. Alternate stepping was restored in the step immediately following the disturbance.

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CHAPTER 4 - SENSORY GATING FOR THE INITIATION OF THE SWING PHASE IN DIFFERENT DIRECTIONS OF HUMAN INFANT STEPPING

4.1 Introduction

Pattern-generating networks are tremendously flexible, capable of producing different motor behaviors (reviewed in Marder and Calabrese, 1996; Marder, 2000). A variety of neuromodulators and input from peripheral and supraspinal sources can modify the neural network to produce different motor patterns (Dickinson, 1989; Getting, 1989; Grillner, 1981; Harris-Warrick, 1991; Marder, 1988, 1991). The same concept has been proposed for the control of locomotion (Clarac, 1984; Grillner, 1981; Pearson, 1993). Direct evidence from the lamprey supports the idea that the same central pattern generator can produce different directions of swimming (Matsushima and Grillner, 1992). Indirect evidence from intact cats suggest that different forms of walking (walk, trot, gallop, upslope, downslope, forward and backward) might be produced by slight alterations of the same pattern generator (Buford and Smith, 1990; Buford et al. 1990, 1993; Carlson-Kuhta et al. 1998; English, 1979; Miller et al. 1975a, b; Perell et al. 1993). Studies in human infants (Lamb and Yang, 2000) and adults (Earhart et al. 2001; Thorstensson, 1986; Winter et al. 1989) also provided indirect evidence that the same neural circuitry controls

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different directions of walking.

Sensory input during rhythmic movements is important for controlling phase transitions such as the transition from stance to swing in walking (reviewed in Rossignol, 1996). In different directions of walking, however, these sensory signals can be very different at the same phase in the movement. For example, in forward walking, hip extension and reduced load are important sensory signals that promote the initiation of the swing phase (Duysens and Pearson, 1980; Grillner and Rossignol, 1978; Hiebert et al. 1996; Pang and Yang, 2000, 2001; Whelan et al. 1995; Whelan and Pearson, 1997). In backward walking, however, swing phase is initiated when the hip is flexed. How does the pattern generator regulate the stance to swing transition in different directions of walking? In both human infants (Lamb and Yang, 2000) and adults (Stein et al. 1986), there is a continuum of walking directions from forward to backward walking. Smooth transitions between different directions of walking are easily performed (Lamb and Yang, 2000). Hence, the processing of sensory inputs must allow for the infinite number of walking directions and the possibility for smooth transitions between them.

In this study, we focus on how different limb orientations that stretch hip muscles and reduce load affect the initiation of the swing phase in forward and sideways stepping in human infants. We use young infants, because they are much less likely to intervene volitionally with the stepping movements compared with adults. Indeed, their stepping is most likely controlled by circuitry in the spinal cord and brainstem (Forssberg, 1985). Our data show that the direction of the limb motion-orientation that most powerfully promotes the stance to swing transition changes with the direction of walking (i.e. hip extension for forward walking, hip adduction in the leading limb and hip abduction in the trailing limb for sideways walking). We propose a conceptual model for selective gating of sensory input as a function of walking direction.

4.2 Materials and methods

4.2.1 Subjects

The infants in this study were recruited through the Public Health Division, Capital Health Authority, Edmonton, Alberta. All of the infants were born at term. Ethical approval was obtained through the Health Research Ethics Board, University of Alberta and the Capital Health Authority, Edmonton, Alberta. Thirty-seven infants aged from 5 to 13 months (mean: 8.4 months) were studied. None of the infants could walk unassisted. The infant's stepping ability was discussed with a parent. Only those infants who showed 10 consecutive steps at a time, as reported by a parent, were brought in for the experiment. The parent was instructed to practice stepping with the infants for 1-2 minutes daily for approximately 1-2 weeks prior to the experiment. Prior work has shown practice improves our chances of obtaining good stepping (Yang et al. 1998). Informed and written consent was obtained from a parent before the infant participated in the study. The experiments were conducted in accordance with the Declaration of Helsinki for experiments on human subjects.

4.2.2 Recording procedures

Kendall SOFT-E, pediatric (Ag/AgCl) electrodes were applied over tibialis anterior (TA) and gastrocnemius-soleus (GS) muscles on each leg after the skin was cleaned with alcohol swabs. A twin-axis electrogoniometer (Penny & Giles Computer Products, Biometrics, Blackwood Gwent, UK) was placed over the hip joint of the right leg (for 22 infants) or the left leg (for 2 infants) or both legs (for 13 infants) to measure hip motion in the sagittal plane (flexion-extension) and the frontal plane (abduction-adduction). The leg recorded from was dependent on the focus of the particular experiment. For example, some experiments focused on comparing the response of the right limb during forward and sideways walking. Others focused on comparing the response of the right and left limb during sideways walking (for details, see Hip disturbances). This was important because infants have a limited tolerance for walking, and only select protocols can be effectively studied in each experiment.

The goniometer was placed so that one arm was aligned with the mid-axillary line of the trunk, and the other was along the longitudinal axis of the femur. A video camera (PV-950; Panasonic, Secaucus, NJ, USA) was used to record the left view (for forward walking) or front view (for sideways walking) of the infant. The video record was used qualitatively for identifying good walking sequences.

A Gaitway treadmill system (Kistler Instrument Corp., Amherst, NY, USA) was used for all experiments. Two force plates located beneath the treadmill belt, one in front of the other, were used to measure vertical ground reaction forces during walking. The infant was held under the arms by one of the researchers, with one hand on each side of the infant's upper trunk, allowing the infant to support its own weight as much as possible. The infant was placed on the treadmill at the junction of the two force plates to allow for accurate measurement of load on each leg during stepping. The speed of the treadmill belt was adjusted to obtain optimal stepping in different directions. If possible, several trials of forward and sideways stepping were conducted for each infant. Each trial was typically 1-3 minutes in length. The whole experimental session took approximately 1 hour. At the end of the session, the weight of the infant was obtained by sitting the infant on the front force plate.

Electromyography (EMG), force plate and electrogoniometer signals were amplified and recorded on VHS tape with a pulse code modulation encoder (A. R. Vetter, Redersburg, PA, USA). All walking trials were videotaped. The video and analog signals were synchronized by a digital counter at a rate of 1 Hz.

4.2.3 Hip disturbances

All of the disturbances were applied manually by a different researcher than the one supporting the infant. The disturbances were intended to stretch a group of hip muscles while simultaneously unloading the leg. A stiff cardboard was placed on the treadmill belt during the swing phase of the limb to be disturbed. After the foot made contact with the cardboard, the leg was dragged in different directions by pulling the cardboard. This allowed us to slide the foot in a direction different from the movement of the treadmill belt. The sliding motion of the cardboard was done as quickly as possible in each direction. The infants were always distracted with toys and games throughout the walking trials. Most infants did not seem to notice the application of the disturbances.

In forward stepping, all perturbations were applied to the right leg. Normally, the hip is extended at swing phase initiation in forward walking. We wished to test whether stretching the hip in the opposite direction (flexion) or a direction orthogonal to the direction of progression (abduction or adduction) would promote or hamper the initiation of the swing phase. Therefore, the right hip was perturbed in four different directions in forward stepping: flexion, extension, abduction, and adduction. In each case, the limb was unloaded by the disturbance.

In sideways stepping, the right leg was always the leading leg in these experiments. The hip of the leading leg is normally adducted at the time swing phase is initiated. We were interested in determining whether hip movement in the opposite direction (abduction) would be less effective in initiating the swing phase. In addition, we wished to determine whether hip extension, the powerful trigger to initiate swing phase in forward stepping, was also effective in sideways stepping. Therefore, three different directions of disturbances were applied to the leading limb: extension, abduction and adduction. Again, the limb was unloaded by the disturbance.

In contrast to the leading limb, the trailing (left) limb normally initiates its swing phase when the hip is abducted during sideways walking. Since hip movements of the leading and trailing limbs are opposite, abduction and adduction disturbances were also applied to the trailing limb to determine whether the leading and trailing limb reacted differently to the two directions of disturbances.

The disturbances described so far involved stretching a group of hip muscles together with unloading the stance leg. We also wished to study the reactions of the leg when the load was high and the hip angle was in a neutral position. Therefore, during both forward and sideways walking, another type of disturbance was used, in which the right hip was kept in a neutral position by holding the cardboard stationary once the limb reached the mid-stance phase (called mid-disturbances). In other words, we prevented the normal hip extension (forward walking) or hip adduction (sideways walking – leading limb) from occurring. Again, we observed whether the swing phase was initiated following the application of these disturbances.

4.2.4 Data analysis

The data were analyzed off-line. The EMG data were high pass filtered at 10 Hz, full-wave rectified and low pass filtered at 30Hz. The force plate and the electrogoniometer signals were also low pass filtered at 30Hz. All the signals were then analog-to-digitally converted at 250 Hz (Axoscope 7, Axon Instruments, Foster City, CA, USA).

The video data were reviewed to identify good sequences of walking and successful disturbances (for definition, see below). The corresponding analog data were then identified. The stance and swing phase durations were estimated by the time of right foot contact and toe off, respectively, using the force plate signals in conjunction with the video image. All the undisturbed steps were selected and averaged using a customized software program.

The EMG, force plate and goniometer signals from undisturbed steps were aligned at the time of foot ground contact. Average profiles were produced for a cycle of stepping. The mean force value over the averaged step cycle gave us an estimate of the amount of weight the infant was bearing during stepping.

The time at which swing phase was initiated was determined by the reversal of the hip goniometer signal from extension to flexion for both directions of stepping. This is reasonable, because when swing phase was initiated in sideways stepping, the reversal of hip motion from adduction to abduction (leading limb) and from abduction to adduction (trailing limb) corresponded well to the reversal from extension to flexion. The corresponding load at the time swing phase was initiated was estimated by the force plate signal.

For all types of disturbances (except mid-disturbances), the beginning of the disturbance was indicated by a sudden change in the goniometer signal in the intended direction. The end of the disturbance was defined as the time when the goniometer signal reached a peak in the intended direction. The angular velocity of hip movement during the perturbation and the duration of the disturbance could thus be computed. The disturbance was considered successful if (1) it was preceded and followed by a complete step, (2) the hip angle between the beginning and the end of the disturbance had a difference of more than 10 degrees, (3) the angular speed of the hip motion was higher than 30 deg/s in the intended direction.

For each type of disturbance, the disturbed leg would react by (1) initiating the swing phase, or (2) continuing its stance phase and not initiating the swing phase until much later. The latency for the initiation of the swing phase was defined as the time period from the beginning of the disturbance to the beginning of the hip flexion movement associated with the swing phase. As the duration of the majority of disturbances ranged from 200 to 500 milliseconds (ms), the swing phase was considered to be successfully initiated if it occurred within 700 ms following the onset of the perturbation. The percentage of trials in which the swing phase was successfully initiated was determined for each type of disturbance. This value was then compared across different groups of disturbances.

4.2.5 Statistical analysis

For each type of disturbance, paired t tests were used to compare the hip angle and load at swing initiation for the pre-disturbed step and those at the end of the disturbance. This was done to make sure that the disturbances applied were effective in changing the hip angle in the intended direction and reducing the load (or increasing the load for mid-disturbances). For comparison of data (i.e. hip angle, load, hip angular velocity of disturbances) between more than two types of disturbances in a given direction of walking or in a given limb in sideways walking, one-way analysis of variance (ANOVA) was used. Bonferroni's t-tests were conducted to compare the data post-hoc. To compare the data between two types of disturbances, independent sample t tests were used. All statistical tests were conducted with mean values from each subject (i.e. averaged across all successful trials). In addition, to compare the proportion of successful trials in eliciting swing phase among different categories of disturbances, Chi-Square test of association was used. A probability level of 0.05 for type-I error was set for all statistical tests. For post hoc t tests, the probability level was adjusted depending on the number of comparisons so as to reduce the probability of making a type-I error (Glass and Hopkins, 1996).

4.3 Results

Of the 37 subjects, 22 subjects participated in both forward and sideways walking. Seven and 8 subjects participated only in forward or sideways walking, respectively. For all trials, the speed of the treadmill ranged from 0.23 m/s to 0.27 m/s. In forward walking, the amount of weight borne by the infants during stepping ranged from 28 to 57% of their own body weight (BW) (mean: 48% BW). In sideways walking, the amount of weight borne by the infants ranged from 16 to 53% BW (mean: 31% BW). For those subjects who participated in both directions of walking, the amount of weight borne during forward walking was significantly greater than that during sideways walking.

Statistical analysis revealed that all types of disturbances were effective in causing a significant deviation of the hip angle in the intended direction when compared to the pre-disturbed steps (Fig. 4-1). Moreover, the deviation in the hip angle for each type of disturbance was significantly different from each other in the intended direction. For example, in forward walking, the hip angle was significantly more flexed after flexion disturbances than that after the other three types of disturbances (Fig. 4-1A). Note that infants adopt a more flexed posture than adults, and the hip rarely extends past the neutral position. In sideways walking, disturbances to the leading and trailing limbs are shown in Fig. 4-1B and 4-1C, respectively. Disturbances in the extension direction included some abduction, because it was important to elicit the extension before the leading limb met the trailing limb at midline.

After the application of different disturbances, there were two types of responses: (1) the limb initiated the swing phase immediately, or (2) the limb continued its stance phase and did not initiate the swing phase until much later. The distribution of latencies for the initiation of the swing phase is shown in Fig. 4-2. The swing phase was successfully initiated in 197 out of 373 trials. For each direction of disturbance, the characteristics of the disturbances (i.e. hip angle, load and speed) were compared between the two types of responses. No significant difference was found. Therefore, the data for each type of disturbance were pooled regardless of the response and then analyzed.

4.3.1 The most powerful input to initiate swing phase changes with direction of walking

The most potent sensory input to promote swing phase initiation was a function of the direction of walking (Fig. 4-3). In forward walking, the most powerful sensory input to trigger the onset of the swing phase was hip extension. Stretching the hip in the opposite direction (i.e. flexion) or in a direction orthogonal to that of progression (i.e. abduction and adduction) resulted in a significantly lower success rate of initiating the swing phase when compared to hip extension (Fig. 4-3, open bars). The results thus indicated that as long as the hip was kept from reaching an extended position during forward stepping, adding an abduction/adduction component did not significantly increase the probability of initiating the swing phase.

An example of an adduction disturbance in forward walking is shown in Fig. 4-4. In all figures, positive numbers in the joint angles represent flexion and abduction. The right hip was adducted to –33°. The limb did not initiate the swing phase until much later when it reached an extended position [see arrow in right tibialis anterior (R TA) EMG signal and the corresponding goniometer signal].

Interestingly, hip extension, which was the most powerful sensory input to initiate the swing phase in forward walking, became relatively ineffective in inducing swing phase in sideways walking. Hip adduction became the most effective input to promote swing phase initiation in the leading limb (Fig. 4-3, solid bars). Similar to the situation in forward walking, adding an orthogonal component (extension) to the leading limb did not increase the likelihood of initiating the swing phase, provided that the hip was not able to attain adduction. An example of an adduction disturbance to the leading limb in sideways walking is shown in Fig. 4-5A. The hip was adducted to –13°. The leg reacted to the disturbance by initiating the swing phase [see early onset of EMG burst in the right tibialis anterior muscle after the disturbance (Fig. 4-5A, arrow in top trace)].

Sideways walking is different from forward walking in that the hip motion of the two legs are opposite in the same phase of the walking cycle. For example, during stance phase, the hip adducts in the leading limb, whereas the hip abducts in the trailing limb. Interestingly, the leading and the trailing leg also showed opposite responses to the different directions of disturbances. Adduction disturbances in the trailing limb typically did not lead to the immediate initiation of swing phase. Fig. 4-5B shows an example of such a disturbance in the same infant as that shown in Fig. 4-5A. The hip is adducted more (-32°) in the trial shown in Fig. 4-5B compared to Fig. 4-5A. In spite of that, initiation of the swing phase was delayed. Group data shown in Fig. 4-3 (cross-hatched bars) indicates that abduction disturbances were far more likely to initiate swing phase than adduction disturbances in the trailing limb.

Could the effects described above be explained by the difference in the amount of unloading and speed of disturbance among different types of disturbances? Our results showed that this possibility was very unlikely. Pooled data for the load at the end of disturbances and the angular speed of hip motion during the disturbances are shown in Fig. 4-6. There was no significant difference in load and speed among the different types of disturbances in a given direction of walking or in a given limb (for sideways walking). Therefore, the results could not be explained by systematic differences in the amount of unloading or the speed of disturbances.

4.3.2 Responses to mid-disturbances

All the results reported so far concerned different directions of hip motion coupled with unloading. We previously reported that during forward walking, if the limb was kept in a mid-stance position, with a neutral hip angle and high load on the limb, swing phase was held off indefinitely (Pang and Yang, 2000). The same was found in sideways walking (Fig. 4-7). During the course of the disturbance, the leading limb was maintained in a slightly abducted position. The disturbed limb remained in the stance phase while the contralateral leg continued to step (reflected in the ongoing rhythmic activity in left tibialis anterior signal).

4.4 Discussion

The response to various directions of disturbances was highly dependent on the direction of walking. The most effective sensory input to promote swing phase initiation for a given direction of walking was leg motion in a direction opposite to that of progression. Interestingly, this meant that, in sideways walking, the reactions in the leading limb were opposite to the trailing limb. While the powerful effects of hip extension to initiate the swing phase in forward walking are well established in both animal (Grillner and Rossignol, 1978; Hiebert et al. 1996) and human infant (Pang and Yang, 2000, 2001) studies, the different reactions of the leading and the trailing legs during sideways walking are now shown for the first time.

4.4.1 Methodological considerations

All the disturbances in this study were applied manually. Variability between disturbances was thus unavoidable. The data showed, however, that we were successful in inducing hip angle changes in the intended direction in all cases, with limited variation (Fig. 4-1). Moreover, other variables that might have affected the success rate for swing phase initiation, such as load on the limb and the angular speed of hip movement, were not significantly different for the different directions of disturbances (Fig. 4-6).

The disturbances displaced the whole lower limb in a particular direction. The induced movements were not confined to the hip, and many types of sensory afferents could have been activated. The limb position at the end of the disturbances, however, was generally very similar for all directions of disturbances (knee extended, ankle plantarflexed), except for the position of the hip. Thus, we feel it is likely that afferents signaling hip position would reflect the different directions of disturbances most. For simplicity in the discussion, we will refer to hip motion when discussing different directions of disturbances. In reality, the results could be explained equally well by a convergence of signals that reflect the limb orientation (Bosco and Poppele, 2001).

The amount of weight borne by the infants during sideways walking was 36% less than that during forward walking. These differences in weightbearing do not interfere with our interpretation, because the comparisons we made were confined to the relative ease with which swing phase was initiated in each direction of walking. We do not compare the unloading necessary for swing initiation in different directions of walking.

4.4.2 Central pattern generators for different directions of walking

Before discussing the nature of sensory gating during different directions of walking, we must first consider whether the same pattern generator controls the different directions of walking. This question has been addressed indirectly in the human adult. Based on comparisons of the muscle activation patterns and the movement patterns, some have suggested that there is sufficient similarity in the patterns to suggest the same pattern generator is involved (Grasso et al. 1998; Thorstensson, 1986; Winter et al. 1989). More recently, Earhart et al. (2001) showed that after walking on the perimeter of a rotating disk, the curved locomotor trajectories of forward and backward walking over stationary ground were very similar. This transfer of learning to both directions of walking supports the idea that forward and backward walking are controlled by similar neural circuitry.

Adult humans, however, can volitionally intervene with the stepping movements, making it difficult to determine the contributions of the lower brain centers to the control of different directions of walking. Since young infants have far less descending control (Forssberg, 1985; Yang et al. 1998), their stepping provides more direct information about the pattern generator. Recent results from our laboratory support the idea that the same pattern generator controls different directions of stepping in young infants (Lamb and Yang, 2000). We showed that the majority of infants can step in all directions from the time forward stepping is expressed. Moreover, changes to the stance and swing phase durations vary in the same way for all directions of walking, and infants can change their stepping in a continuous way from forward to backward.

4.4.3 Selective gating of sensory input

Our current results show that the same sensory input produces a very different response that is a function of the walking direction. Thus, there must be gating of sensory input that is a function of the walking direction. Based on the assumption that the same locomotor pattern generator controls all directions of walking, the experimental evidence presented in this paper predicts that there is a large convergence of sensory input to the pattern generator. Afferents that signal various hip positions (or limb orientations), for example, should all have access to the pattern generator.

Depending on the direction of walking, the gains in these pathways are selectively altered.

Using the half-center model for locomotion (Brown, 1911, 1914; Lundberg, 1980), we propose a conceptual model where there is convergence of sensory input from the legs to the flexor and extensor half-center. Our data suggest that load always influences the decision to initiate swing phase, regardless of the direction of walking. Afferents signaling hip position (or limb orientation) are selectively gated as a function of the walking direction. For example, in forward walking, gains in reflex pathways from stretch-sensitive afferents in hip flexor muscles are higher than those from other hip muscles. During sideways walking, the reflex gains from stretch-sensitive afferents in hip abductors to the pattern generator are higher in the leading limb, while those from hip adductors are higher in the trailing limb. We further predict that with walking directions intermediate between forward and sideways, the reflex gains from stretch-sensitive afferents in hip flexors and abductors of the leading limb would be higher than those from other hip muscles. Thus, the most effective stretch to initiate the swing phase in this case would be a combined hip extension and adduction (i.e. directly opposite to the direction of walking).

Previous studies have shown that transmission in reflex pathways is highly dependent on the form of the task (reviewed in Rossignol, 1996). For example, the phase-dependent responses to cutaneous stimulation of the leg in forward walking are different from those in backward walking (Buford and Smith, 1993; Duysens et al. 1996). Based on the pattern of reflex modulation, Duysens et al. (1996) suggested that their results from backward walking could be explained by a reversal of the motor program that produces forward walking. No details were given regarding how this might be achieved. Our current results suggest that we must consider the changes in reflex gain from forward to backward walking as a continuum, which must account for all directions of walking in-between. With this in mind, the models proposed must also reflect the continuum of walking directions.

Taken together, these results lend support to the idea that the human nervous system uses sensory input in a probabilistic way to make motor decisions. The relative weighting of many different sensory inputs are used in the final decision (Bassler, 1993; Prochazka, 1996a, b; Prochazka and Yakovenko, 2001). In this way, sensory input related to different directions of hip motion all contribute to the motor decision of whether or not to initiate the swing phase. Indeed, swing phase can still be initiated when the hip position was not optimal (Fig. 4-3), but at a reduced probability.

To our knowledge, this is the first report to show that different sensory signals control the stance to swing transition for different directions of walking in humans. The results indicate the presence of selective gating of sensory input as the direction of walking changes. We further predict that the mechanism for selecting the sensory signals must form a continuum to account for the continuum of walking directions possible in humans.

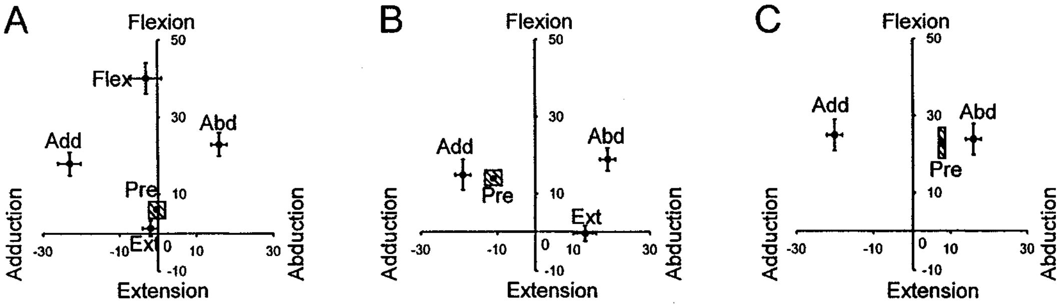

Figure 4-1. Pooled data: hip angle at the end of disturbances
The final hip angle achieved at the end of disturbances is shown for forward walking (**A**), the leading limb in sideways walking (**B**), and the trailing limb in sideways walking (**C**). The horizontal axis represents the hip abduction-adduction angle, and the vertical axis represents hip flexion-extension angle. The label beside each data point represents the direction of the disturbance (Flex: flexion; Ext: extension; Abd: abduction; Add: adduction). The error bar represents one standard error. The shaded box labeled "Pre" represents one standard error for the normal steps preceding the disturbance. The data show that we were successful in altering the hip angle in the intended directions.

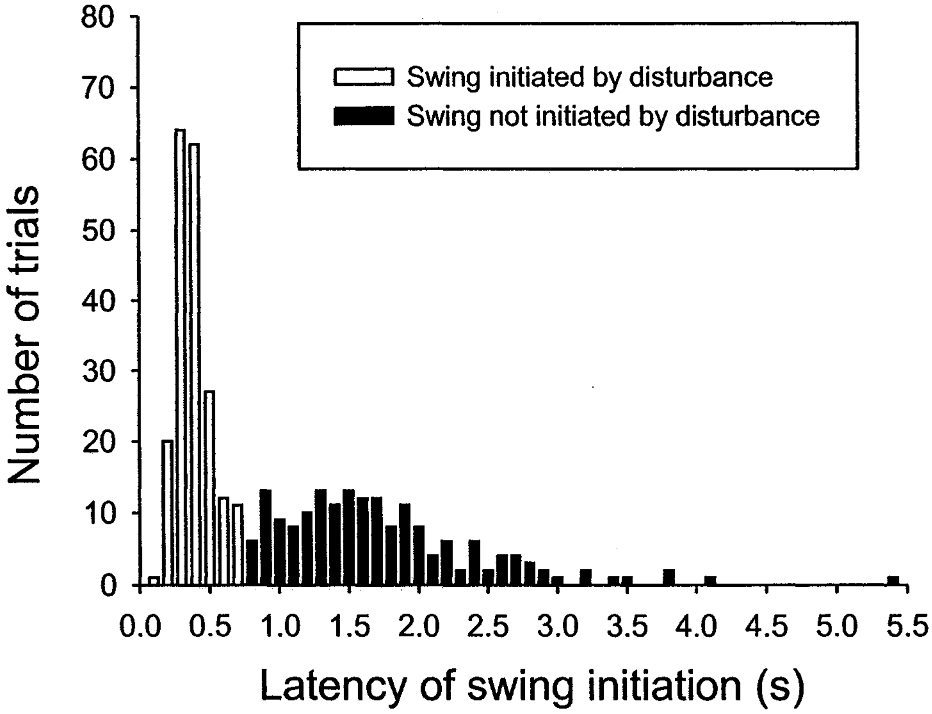

Figure 4-2. Latencies for the initiation of the swing phase
The open bars represent those trials in which the swing phase was successfully initiated by the disturbance (within 700 ms following onset of the perturbation). The black bars represent those trials in which the disturbed leg continued with its stance phase after the disturbance and did not initiate its swing phase until much later.

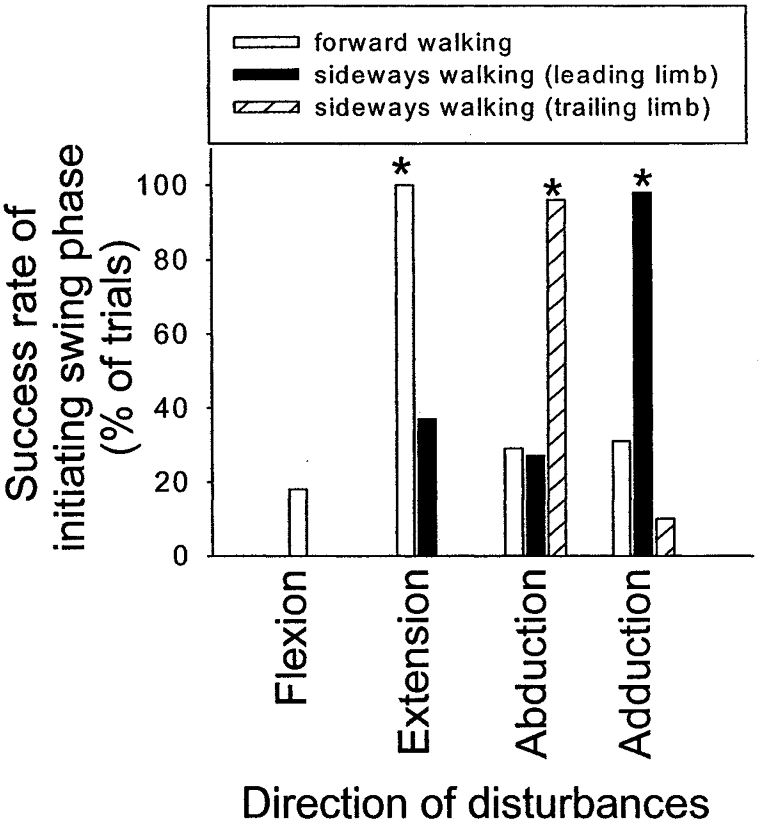

Figure 4-3. Success rate of initiating the swing phase
In forward walking, hip extension was the most powerful sensory input to initiate the swing phase. In sideways walking, hip adduction and hip abduction became the most potent input to induce the onset of the swing phase in the leading limb and trailing limb, respectively. Asterisks represent a statistically significant difference from the other types of disturbances in the same direction of walking or in the same limb (for sideways walking).

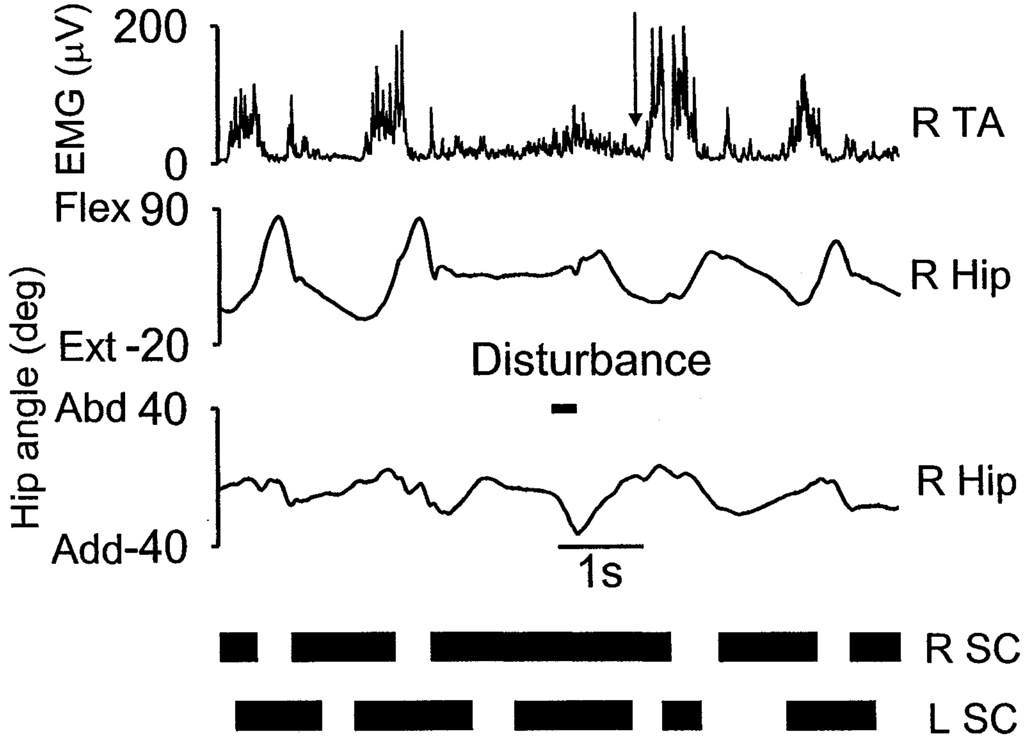

Figure 4-4. Example of an adduction disturbance in forward walking
Surface electromyography (EMG) from the right tibialis anterior, goniometer measures of the right hip, and step cycles (SC) of both legs are shown for a single subject (LG). The thick line between the second and the third traces represents the duration of the disturbance. The black bars at the bottom of the graph represent stance phase, whereas the space between the bars represents swing phase. In this particular example, the right hip was adducted to –33° by the disturbance. Swing phase was not initiated until much later when the hip reached an extended position (see arrow in R TA signal and the corresponding hip flexion seen in the goniometer signal). The right stance phase was prolonged as a result.

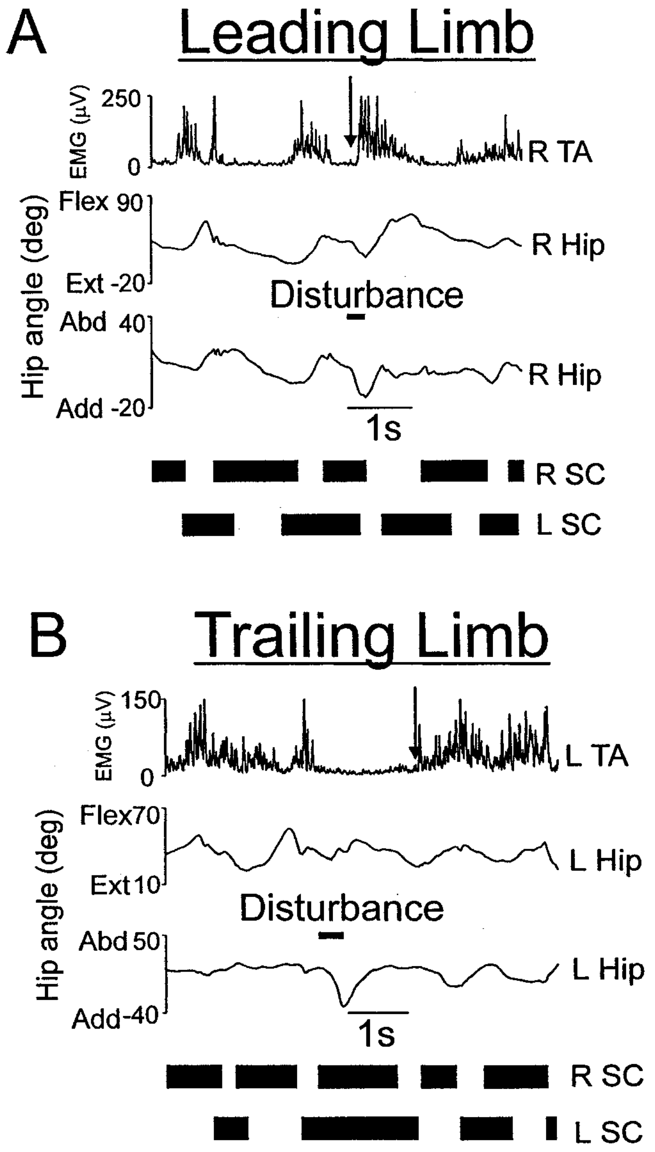

Figure 4-5. Example of adduction disturbances to the leading and trailing limbs in sideways walking

Data in both parts of the figure are from the same infant (subject EO). The convention of this figure is the same as Figure 4-4. **A.** Response of the leading leg to a disturbance that adducted the hip to –13°. The swing phase was initiated early (see arrow in R TA signal). **B.** Response of the trailing leg to a disturbance that adducted the hip to –32°. In this case, swing phase was delayed.

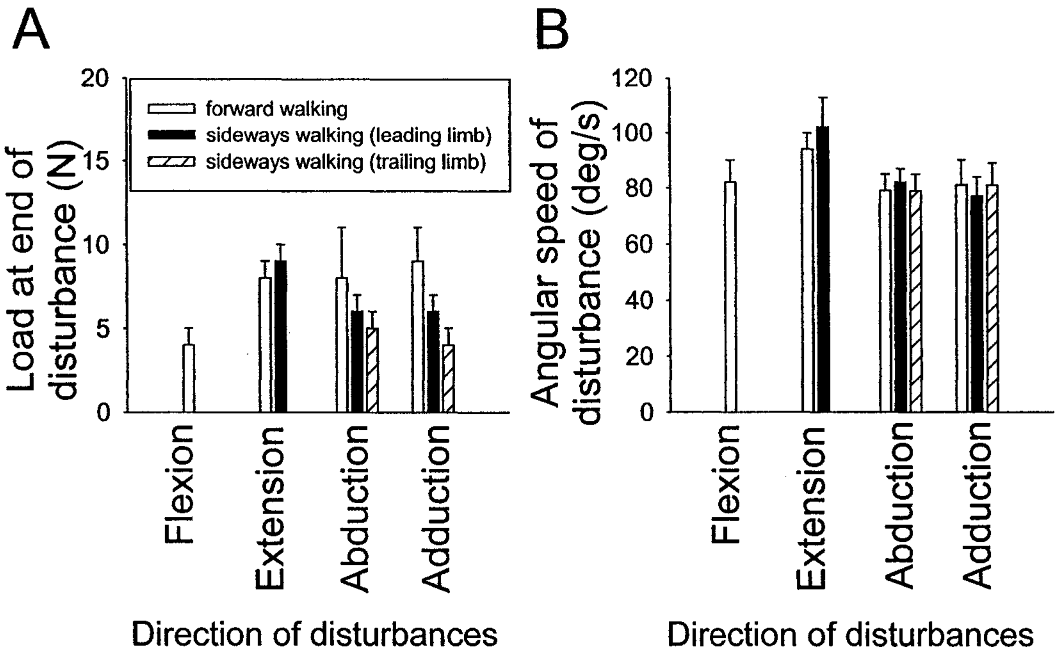

Figure 4-6. Pooled data: load at the end of disturbances and speed of disturbances

A. Load at the end of disturbances and **B.** the angular speed of the hip motion during the disturbances. There was no statistically significant difference in load and speed among the different types of disturbances in a given direction of walking or in a given limb (for sideways walking).

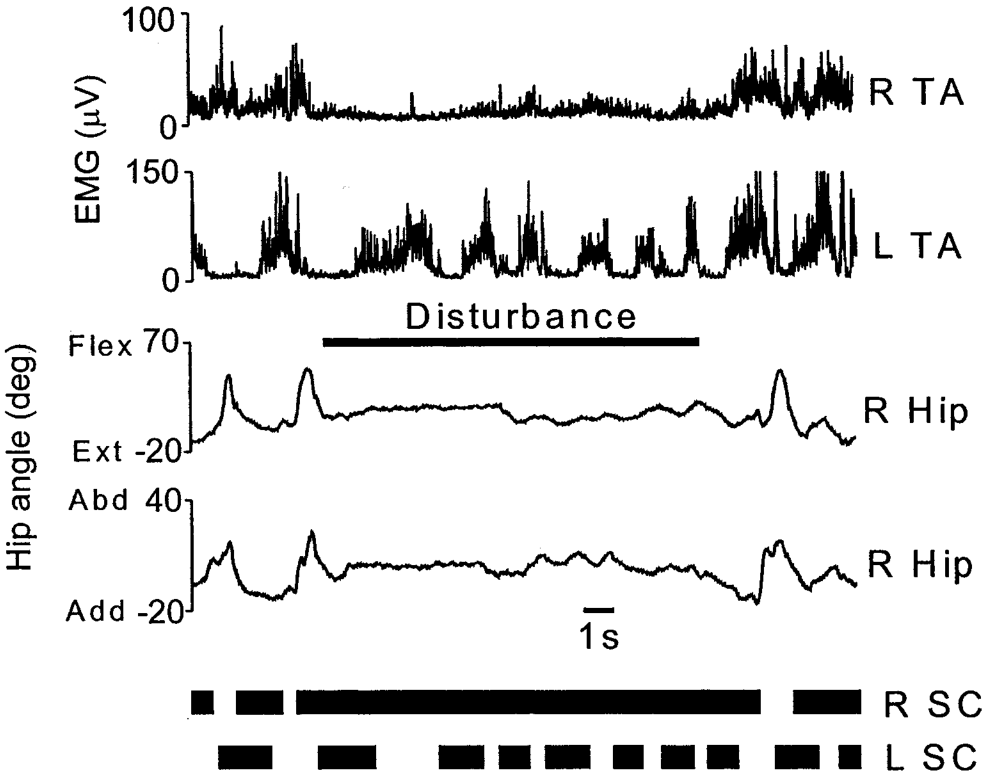

Figure 4-7. An example of a mid-disturbance in sideways walking
Responses from a single subject (ML). Convention of the figure is the same as Figure 4-4. The hip was kept in a slightly abducted position (mean: 4°) and the load was high (mean: 28 N, data not shown). As a result, the stance phase was prolonged. The normal alternating activity of right tibialis anterior was terminated. In contrast, the left leg continued to step (see ongoing alternating activity in the left tibialis anterior).

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CHAPTER 5 – INFANTS LEARN TO ADAPT THEIR STEPPING TO TRIP-INDUCING STIMULI

5.1 Introduction

Adult humans can adapt to sustained changes in the environment by modifying their movement patterns to meet their behavioral goals (Flanagan et al. 1999; Gondolfo et al. 1996; Martin et al. 1998a, b, 2002). For example, when subjects were asked to move a hand manipulandum to reach visual targets, they chose a straight trajectory from the initial position to the target. When a perturbing force field was introduced to the manipulandum, the trajectory of arm movement became perturbed by the force field. With practice, the trajectory resumed the original shape as if there was no perturbation. Immediately upon removal of the force field, the trajectory became a mirror image of the initial trajectory when the force field was first introduced, revealing a compensatory response, called after-effect. The presence of after-effects reflects the ability of the subjects to predict the disturbances and modify the motor program to cancel the effects of the perturbations (Gondolfo et al. 1996).

After-effects have also been reported during locomotion. Following a period of walking on a rotating disk, blindfolded human subjects showed curved walking trajectories when attempting to walk in a straight line (Earhart et al. 2001; Gordon et al. 1995; Weber et al. 1998). After running forward on a treadmill, blindfolded subjects inadvertently jogged forward when asked to jog in place (Anstis, 1995). Similarly, after running on a treadmill that sloped upward, the horizontal treadmill belt was perceived as sloping downward (Anstis, 1995). Jensen et al. (1998) also reported that after a period of walking on a split-belt treadmill with the belts running at different speeds, the subjects were unable to perceive and equalize the speeds of the belts totally. These data show that the adult human locomotor system is capable of adaptive plasticity following exposure to sustained perturbations.

Reduced mammalian preparations also show adaptation to repeated perturbations during walking. In decerebrate ferrets, decerebrate cats and spinal cats, when the swing phase of the forelimb was repeatedly perturbed by a bar (i.e. trip-inducing stimuli), the animal learned to increase the maximum height of the limb during the swing phase to avoid the obstacle. Upon removal of the obstacle, the high stepping persisted for several step cycles (Bloedel et al. 1991; Edgerton et al. 2001; Hodgson et al. 1994; Lou and Bloedel, 1987). These results suggest that this particular form of learning does not require the cerebrum.

Would the human subcortical locomotor circuitry show similar phenomenon? Human infants have been used as a model to study subcortical control of walking in humans (Yang et al. 1998). In this study, we examined whether human infants under the age of 1 year adapt to repeated trip-inducing stimuli during the swing phase of stepping. Our data showed that the high stepping persisted for a few steps following the removal of trip-inducing stimuli, primarily in infants older than 10 months of age. The results suggested that the locomotor circuitry in infants is capable of adaptive plasticity, but is likely dependent on the maturation of specific neural structures.

5.2 Methods

5.2.1 Subjects

The infants in this study were recruited through three local health clinics. Ethical approval was obtained through the Health Research Ethics Board, University of Alberta and Capital Health, Edmonton, Alberta. Parents were contacted by phone and instructed to practice stepping with the infant for 1 - 2 minutes daily because practice has been shown to increase the chance of obtaining good stepping in the laboratory (Yang et al. 1998). We contacted the parent/guardian monthly to determine whether the infant was stepping. The infant was brought in for the experiment if the parent or guardian reported that the infant can make at least 10 consecutive steps with support at a time. Informed and written consent was obtained from the parent before the infant participated in the study. The experiments were conducted in accordance with the Declaration of Helsinki for experiments on human subjects. Thirty-three infants aged 5 to 11 months (mean: 9.1 months) were studied. All of the infants were born at term. None of the infants could walk unassisted at the time of the experiment.

5.2.2 Recording procedures

After the skin was cleaned with alcohol swabs, Kendall SOFT-E, pediatric (Ag/AgCl) electrodes were applied over four muscle groups in the left leg: quadriceps (Q), hamstrings (HAMS), tibialis anterior (TA), and gastrocnemius-soleus (GS). An electrogoniometer (Penny and Giles Computer Products, Biometrics, Blackwood Gwent, UK) was placed over the left knee joint to measure knee motion in the sagittal plane (flexion-extension). The goniometer was placed so that one arm was aligned with the longitudinal axis of the femur and the other with the lower leg. Adhesive skin markers were placed over the left side of the trunk just above the superior border of the iliac crest, the greater trochanter, the knee joint line, the lateral malleolus and the lateral aspect of the fifth metatarsal-phalangeal joint of the left leg. The left view of the infant was recorded (30 frames per second) by using a video camera (PV-950; Panasonic, Secaucus, NJ, USA).

A Gaitway treadmill system (Kistler Instrument, Amherst, NY, USA) was used for all experiments. Beneath the treadmill belt were two force plates, one in front of the other, to measure vertical ground reaction forces during walking. To prevent the infant from seeing the baton that was used to induce tripping, a linen sheet was placed approximately 20cm above the treadmill surface surrounding the infant. The infant was held under the arms by one of the researchers or by a parent, with one hand on each side of the infant's upper trunk. The forearm of the individual holding the infant was supported to ensure that no movement was imposed on the infant. The infant was allowed to support its own weight as much as possible. The speed of the treadmill belt was adjusted to obtain optimal stepping (between 0.23 m/s and 0.32 m/s). Several trials of forward stepping were recorded for each infant.

Trip-inducing stimuli were applied manually. In previous animal studies (Edgerton et al. 2001; Lou and Bloedel, 1987), disturbances were elicited by interjecting a bar into the path of the limb on each successive swing phase. Because the stepping pattern is more variable in infants, placing the bar in the same location would not have provided consistent perturbations. For example, the position of the limb varies mediolaterally with each step and the onset of the swing phase varies. For these reasons, the bar may make contact with different parts of the foot at different times in the swing phase. Therefore, we applied the trip-inducing disturbances manually to make sure the perturbations were applied to the correct location of the foot (i.e. dorsum) at the desired part of the step cycle (i.e. early swing). An instrumented baton with a sponge-covered tip was used to briefly touch the dorsum of the left foot during the early swing phase. The baton was instrumented with a force transducer to measure the amount of force applied to the foot during the disturbance. In some trials, only one swing phase was disturbed. In other trials, the foot was touched for a few consecutive steps (varying from 2 to 6 steps, randomly). Typically, the mechanical stimulus induced a stumbling corrective reaction. We observed whether high stepping persisted after the removal of the trip-inducing stimuli (i.e. after-effect). Trials with trip-inducing stimuli were repeated as much as possible, depending on the tolerance of the infant.

Throughout the experiment, infants were distracted with games and toys. Each walking trial was typically 1 - 2 minutes long. The whole experimental session took approximately 1 hour. Electromyography (EMG), signals from the baton, force plates, and knee electrogoniometer were amplified and recorded on VHS tape with a pulse code modulation encoder (A. R. Vetter, Redersburg, PA, USA). All walking trials were videotaped. The video and analog signals were synchronized by a custom-made digital counter at a rate of 1 Hz. At the end of the session, the mass of each infant was recorded [(range: 7.3 - 12.5 kilograms (kg)].

5.2.3 Data analysis

The data were analyzed off-line. The EMG data were high pass filtered at 10 Hz, full-wave rectified and low pass filtered at 30Hz. The signals from the baton, force plates and knee electrogoniometer were also low pass filtered at 30Hz. All the signals were then analog-to-digitally converted at 250 Hz (Axoscope 8; Axon Instruments, Foster City, CA, USA).

The video data were reviewed to identify sequences of walking and disturbances. The corresponding analog data were then identified. The beginning of the stance and swing phases were determined by foot contact and toe off, respectively, as indicated by the force plate signals in conjunction with the video image. In order to obtain baseline measures of joint movements and toe clearance, ten undisturbed steps were randomly chosen to serve as the control for each subject. For selection of successful disturbances, the following criteria were used: (1) the force signal from the baton reached its peak during early swing phase (i.e. before the knee goniometer signal reversed from flexion to extension), and (2) the peak disturbance force exceeded 0.5 Newton (N), because we found that a force of 0.5 N was sufficient to elicit a high step, and (3) the sequence of the disturbances was followed by at least five consecutive undisturbed steps, because we wished to determine the time course of any high stepping following the removal of the stimuli.

The peak force value recorded from the baton was used as a measure of the force applied to the foot during the disturbance. If more than one disturbance was applied in a trial, the peak force of each disturbance in that trial was summed and then averaged. This value thus served as an estimate of the average peak force applied to the foot for that particular trial. Since the disturbance was applied during the swing phase and the subsequent modifications in locomotor trajectory occurred primarily in the swing phase, the data analysis focused on the swing phase.

The relevant video data (i.e. the swing phases of the control steps, disturbed steps and 5 post-disturbed steps) were digitized from the videotape to the computer (Adobe Systems Inc., Mountain View, CA, USA). The positions of the joint markers were digitized manually using custom-written software programs (Frame Analyzer, Garand International Telecom. Ltd.). The position data were then filtered using a 4th order Butterworth, dual-pass filter with a low-pass cut-off frequency at 6 Hz (Winter, 1991). The maximum toe height (as indicated by the position of the joint marker on the left 5th metatarsal-phalangeal joint), and the angles of the left hip, knee and ankle joints were computed with custom-written software programs (MATLAB; MathWorks, Natick, MA, USA).

We were also interested in determining whether the adaptive changes in movement pattern following the removal of the stimuli were reflected by changes in muscle activity. Mean EMG amplitude of the TA burst for the whole duration of the swing phase was calculated for the control steps and the five post-disturbed steps. It was very difficult to record from the hip and knee flexor muscles from the infants because of the deep location of the muscles and the considerable amount of fatty tissue in the area, resulting in a small signal to noise ratio. In order to estimate the changes in muscle activity at the hip and knee joints during the swing phase, inverse dynamic analysis was performed to estimate muscle torques at the hip and knee.

Out of plane movements were determined by changes in the apparent lengths of the thigh and lower leg using the video data. If the apparent length of the thigh or lower leg varied by more than 10% during the swing phase, the step was eliminated from kinetic analysis. Only 9% of the steps were excluded as a result. Inverse dynamic analysis using a 2-segment model (i.e. lower leg and foot were considered as one segment) was performed to calculate the hip and knee torques (Hoy and Zernicke, 1986). This was reasonable, because the mass of the foot and the force contribution from the ankle are very small in the swing phase (Schneider et al. 1990; Lam et al. 2003). The torque values were normalized to the mass of the infant (Winter, 1991). Muscle torques were evaluated for all control steps and the first post-disturbed steps only, because any adaptive changes in stepping would be most apparent in the first post-disturbed step. Because there was variability in the swing phase duration between and within subjects, the swing phase duration was normalized in order to allow data averaging and comparison between trials and between subjects. Custom written software (MATLAB) was used for all evaluations.

5.2.4 Control experiments

Control experiments were conducted with 5 infants to make sure that the after-effect was not due to heightened excitability of the infants caused by the repeated stimuli. The trip-inducing stimuli were applied in the same way as previously described. In addition, separate trials were recorded in which mechanical taps were applied to the posterolateral aspect of the left thigh with the same baton. In both cases 2 to 6 consecutive disturbances were applied (see Results, Fig. 5-3). If the after-effect was due to an increase in general excitability caused by repetitive sensory stimulation, it should not matter where the stimuli were applied in the leg.

5.2.5 Statistical analysis

For each trial, one-tailed z-tests were used to determine whether the maximal toe height for the first post-disturbed step was significantly higher than that from the averaged control steps. Z-score is a ratio of the difference in maximum toe height (between the first post-disturbed step and the averaged control steps) and the standard deviation of the maximum toe height for the averaged control steps. An after-effect was defined as a z-score higher than 1.645 ($p = 0.05$). If repeated trials were available, the z-score for each trial was summed and averaged. The subject is considered to have an after-effect if the average z-score exceeds 1.645. One way analysis of variance (ANOVA) was used to determine whether the force applied to the foot was significantly different between trials with different number of consecutive disturbances (varying from 1 to 6). Chi-square test of association was used to test the relationship between the incidence of after-effect and number of perturbed step cycles. Because older (> 10 months) and younger infants (< 8 months) seemed to show a different response following the removal of trip-inducing stimuli, Chi-square test of association was also used to test whether there was an association between the incidence of after-effect and the two different age groups. Paired t-tests were used to compare the control steps and the post-disturbed steps in (1) maximum toe clearance, (2) hip muscle torque, (3) knee muscle torque and (4) mean TA EMG amplitude. Two-way ANOVA was used to determine whether the average peak force of the disturbances and the average maximum toe height for the disturbed steps were different between subjects who showed an after-effect and those who did not. This comparison was done with the number of consecutive disturbances as the second factor in the ANOVA. Single disturbances were not included in the analysis, because it produced very few after-effects in both groups. The statistical tests were conducted with mean values from each subject (i.e. averaged across all successful trials). A significance level of 0.05 for type-I error was set for all statistical tests.

5.3 Results

5.3.1 Some infants showed high stepping following removal of trip-inducing stimuli

Some infants continued to show high stepping following the removal of the trip-inducing stimuli. Data from a single subject are shown in Figure 5-1. The black bars (4th trace in Fig. 5-1A) represent the stance phases of the left leg whereas the spaces between the bars represent the swing phases. The maximum toe height during swing phase is indicated in the bottom trace. Each data point represents one single step. The data points between the vertical dashed lines indicate the disturbed steps. In this particular example, three consecutive swing phases were perturbed (see the corresponding force signal from the baton in the 3rd trace). The left leg reacted to the perturbations by producing high steps as indicated by the maximum toe height (bottom trace) and the increase in knee flexion angle (2nd trace). The maximum toe height did not return to control value until the 3rd post-disturbed step. The stick diagrams show the trajectory of the left leg for the last undisturbed step before the disturbances (pre-disturbed step) (Fig. 5-1B), the first disturbed step (Fig. 5-1C) and the first post-disturbed step (Fig. 5-1D). It is obvious that the movement pattern was modified in the first post-disturbed step when compared to the pre-disturbed step.

On the other hand, some infants did not show any after-effect following repeated trip-inducing stimuli. An individual example is shown in Figure 5-2. In this case, six consecutive swing phases were perturbed (Fig. 5-2A). Similar to the previous example, the infant reacted to the disturbances by producing high steps. However, immediately following the removal of the disturbances, no high stepping was observed. The maximum toe clearance for the first post-disturbed step immediately returned to control value. The stick figures illustrate the whole movement pattern. High stepping was elicited by the disturbance (Fig. 5-2C), but the movement trajectory for the first post-disturbed step (Fig. 5-2D) was very similar to that for the undisturbed step (Fig. 5-2B), indicating the absence of an after-effect.

5.3.2 Incidence of after-effect and number of disturbed step cycle

Figure 5-3A shows the relationship between the number of consecutive disturbances applied in a given trial and the percentage of trials in which an after-effect was successfully induced. Data from all infants are included. When a single swing phase was perturbed, after-effects were rarely seen. As the number of consecutive disturbances was increased to two, after-effects were observed more frequently. The success rate of inducing an after-effect remained more or less the same as the number of consecutive disturbances was further increased up to six. There was a significant association (Chi-square test of association, $p<0.05$) between the number of perturbed step cycles and the incidence of an after-effect. The average peak force applied to the foot was the same regardless of the number of consecutive disturbances (one-way ANOVA), so differences in force were not a factor in the generation of after-effects (Fig. 5-3B).

5.3.3 Incidence of after-effect and age

There was a correlation between the presence of an after-effect and age. Data were pooled for all trials with 2 or more disturbances in an infant, since there was no difference in the response between disturbances of 2 or more (number of trials per subject: median: 5, mean: 6). The pooled data were plotted so that the horizontal axis represents the age of the infants while the vertical axis indicates the z-score for average maximum toe height in the first step after the disturbance was removed

(Fig. 5-4). Each data point thus represents the data from one infant. The dashed line in the figure indicates the z-score value of 1.645. Data points above the line indicate a significant after-effect. Despite variability between subjects, the z-scores showed a tendency to increase with age. Most of the infants older than 9 months of age (71%) and few of the infants younger than 9 months of age (20%) demonstrated an after-effect.

The infants were further divided into two groups: those younger than 8 months and those older than 10 months (Fig. 5-5). For each group, the number of infants with and without an after-effect was plotted against the number of consecutive disturbances applied in a given trial (Number of trials per subject for each category of disturbance: median: 2, mean: 2). For the younger infants, after-effects were rarely seen, regardless of the number of disturbances applied (Fig. 5-5A). In contrast, for the older infants, the probability of obtaining an after-effect was increased if more than 1 disturbance was applied (Fig. 5-5B). There was a significant difference in the incidence of obtaining an after-effect between the two groups of infants, for trials in which 3 or more consecutive disturbances were applied (Chi-square test of association).

Could the relationship between the z-score and age be due to a less variable stepping pattern in the older infants? Using trials in which 2 or more consecutive disturbances were applied, the average increase in toe clearance for the first post-disturbed step compared to control steps for the older infants (4.5 cm), which was 2 times higher than the younger infants (2.1 cm). The mean standard deviation of the maximum toe height for the control steps was 1.4 and 1.7 cm respectively, for the infants older than 10 months and those younger than 8 months, indicating that the younger infants were only slightly more variable than the older infants.

Could the difference in obtaining an after-effect result from the difference in the amount of force applied to the foot? The pooled data (Fig. 5-6A) showed that there was no significant difference in force between the infants with an after-effect (solid bars) and those without an after-effect (open bars) regardless of the number of consecutive disturbances applied (two-way ANOVA). Is it possible that the two groups of infants responded to the disturbances differently, and as a result exhibited differences in the after-effect? The maximum toe height achieved was compared between infants that showed an after-effect and those that did not. There was no systematic trend in this comparison, although in two comparisons (i.e., 4 and 5 consecutive disturbances) the two groups were significantly different (Fig. 5-6B).

5.3.4 Time course of after-effect

Pooled data across subjects showed that the after-effect was relatively short-lived, varying from 2-4 step cycles. No definite relationship between the length of the after-effect and the number of perturbed step cycles could be identified. Figure 5-7 illustrates the maximum toe clearance for the infants who showed an after-effect following the application of 2 (Fig.

5-7A) and 6 disturbances (Fig. 5-7B). The averaged control steps, disturbed steps and the five post-disturbed steps are shown. In both cases, after the trip-inducing stimuli were removed, high stepping persisted for another 4 step cycles before the toe clearance returned to the control value.

5.3.5 Kinematics

Kinematic analysis revealed that the high stepping following the removal of the trip-inducing stimuli was produced by an increase in hip and knee flexion. Pooled data for the trials in which 2 to 6 consecutive swing phases were disturbed is illustrated in Figure 5-8. Hip angle (Fig. 5-8A & D), knee angle (Fig. 5-8B & E) and toe height (Fig. 5-8C & F) are plotted against the percentage of normalized swing phase duration (0% represents toe-off while 100% represents foot-floor contact). For those infants who did not demonstrate an after-effect (left panels, Fig. 5-8A, B & C), the hip and knee angle and toe height for the first post-disturbed steps (thick lines) were quite similar to those for the control steps (thin lines). A slight increase in knee flexion and toe clearance is noted, probably because a number of infants in this group showed an increase in toe clearance but barely missed the significance level of 0.05 (Fig. 5-4). In contrast, for those infants who demonstrated an after-effect, the movement during the swing phase of the first post-disturbed step was characterized by an increase in hip and knee flexion (right panels, Fig. 5-8

D, E & F). Note that the knee flexion angle peaked slightly earlier than the hip flexion angle.

5.3.6 Muscle torques

The after-effect was also seen as an increase in hip and knee flexor muscle torques during swing phase. The average hip and knee muscle torque profiles during the swing phase are shown in Figure 5-9. For infants without an after-effect, the hip and knee torque profiles for the first post-disturbed steps (thick lines) were quite similar to those for the control steps (thin lines) (Fig. 5-9A & B). In contrast, for infants with an after-effect, there was a large increase in the knee flexor torque in the early swing phase, followed by an increase in hip flexor torque (Fig. 5-9C & D).

The mean amplitude of the left TA EMG burst during the whole swing phase was also measured. Overall, there was no significant increase in TA EMG amplitude between the averaged control step and the first post-disturbed step for infants with an after-effect and those without (not shown).

5.3.7 Control experiments

The results for the control experiments are shown in Figure 5-10. All of the infants reacted to the trip-inducing stimuli to the dorsum of the foot by increasing their toe clearance during the swing phase ($z > 1.645$). In contrast, none of the infants responded to the thigh stimulation by producing high steps. More importantly, while four out of five infants showed an after-effect in the first post-disturbed step after the trip-inducing stimuli were removed, none of the infants showed an after-effect following the removal of thigh stimulation. The average force applied to the dorsum of the foot (3.4 N, S.E.M. = 1.5 N) was not significantly different from that applied to the thigh (3.2 N, S.E.M. = 1.5 N).

5.4 Discussion

Our main finding is that older infants (> 9 months old) learned to adapt to trip-inducing stimuli by generating high steps even after the stimulus was removed. The results indicate that the locomotor circuitry in human infants is capable of adaptive plasticity, particularly after the age of 9 months.

5.4.1 Methodological considerations

The trip-inducing perturbations were applied manually. Variability between disturbances was inevitable. Efforts were made to ensure that we were as consistent as possible in applying the disturbances. For example, the same researcher applied all the disturbances in this study, the force applied to the foot was quantified by a force transducer, and criteria were set to guide our selection of successful disturbances (see Methods). With these controls, the data showed that the variability in the disturbance force between subjects was small (Fig. 5-3B). There were no significant differences in force between the infants with an after-effect and those without (Fig. 5-6A).

The results also showed that the difference in variability of stepping between the older and younger infants cannot account for the difference observed in after-effects in the two groups. The standard deviation of the maximum toe trajectory was very similar between the two groups. The two groups of infants also responded similarly to the disturbances (Fig. 5-6B), with only 2 of the 5 comparisons being different. Thus, it is unlikely that the two groups responded differently to the touch stimuli. Finally, the control experiments indicated that it is unlikely that the after-effect was due to an increase in general excitability produced by repetitive mechanical stimuli (Fig. 5-10). In summary, the presence of after-effects in babies cannot be attributed to methodological problems.

5.4.2 Modifications in the movement pattern in response to repeated stimuli

The results clearly showed that some infants modified their motor program with repeated stimuli. The modified movement pattern is very similar to the high steps generated during the disturbed steps (Fig. 5-1B & 2B). Moreover, the movement pattern resembles the "elevating strategy" in adult humans when the dorsum of the foot strikes an obstacle during early swing phase (Eng et al. 1994). Similar to adult humans, the response in human infants is characterized by an increase in knee flexion, followed by an increase in hip flexion in the swing phase (Fig. 5-8B & D), thereby increasing the foot clearance (Fig. 5-8F). The kinematic changes result from an increase in knee flexor torque first, followed by an increase in hip flexor torque (Fig. 5-9B & D). The adaptation is functionally appropriate in that it first moves the limb away from the obstacle (knee flexion) and then over the obstacle (hip flexion) (Eng et al. 1994).

5.4.3 Are lower centers of human CNS capable of adaptive locomotor plasticity?

Decerebrate ferrets and cats showed high stepping immediately following the removal of repeated trip-inducing stimuli (Bloedel et al. 1991; Lou and Bloedel, 1987), indicating that this form of learning does not require the cerebrum. When the cerebellum was also removed from decerebrate ferrets, they showed the same learning behavior, although the movement was reported to be more disorganized (Bloedel et al. 1991). This finding suggested that the cerebellum, while necessary for co-ordination of smooth movements, is not essential for this type of learning either. In addition, it has been reported that spinal cats show the same phenomenon (Edgerton et al. 2001; Hodgson et al. 1994). Unfortunately, only single subject data were presented in their reports. It is thus difficult to determine whether after-effects can be consistently obtained in all spinal cats. Thus, whether the mature spinal cord is capable of this form of learning remains an open question.

It has been well known that the isolated spinal cord is capable of other forms of learning, as demonstrated in experiments studying habituation and sensitization of spinal reflexes (Durkovic, 1975, 1986; Kandel, 1977; Lloyd, 1949; Steinmetz et al. 1981) and classical conditioning (Durkovic, 1975, 1986; Durkovic and Damianopoulos, 1986; Dykman and Shurrager, 1956; Grau and Joynes, 2001; Kandel, 1977). The spinal cord is also able to learn specific functional tasks (i.e. stepping, standing) depending on the specific training regimen (de Leon et al. 1998a,b; Edgerton et al. 1992, 1997; Hodgson et al. 1994; Lovely et al. 1986; Viala et al. 1986). Moreover, following peripheral nerve injury, spinal cats are capable of significant locomotor recovery (Bouyer and Rossignol, 1998, Bouyer et al., 2001; Carrier et al. 1997). Therefore, spinal learning can occur under many different experimental conditions.

Our results showed that some infants increased their toe clearance following the removal of repeated, trip-inducing stimuli, just as in the reduced animals. It has generally been assumed that the stepping response in human infants is largely controlled by the brainstem and the spinal cord (Forssberg, 1985; Peiper, 1963). The cerebrum and its descending motor pathways to the spinal cord are not mature before the age of one year, as demonstrated by histological (Altman and Bayer, 2001; Brody et al. 1987; Kinney et al. 1988; Yakovlev and Lecours, 1967), electrophysiological (Crum and Stephens, 1982; Evans et al. 1990; Eyre et al. 1991; Issler and Stephens, 1983; Koh and Eyre, 1988; Mayer and

Mosser, 1969, 1973; Muller et al. 1991; Nezu et al. 1997; O' Sullivan et al. 1991; Vecchierini-Blineau and Guiheneuc, 1981) and radiological studies (Barkovich et al. 1988; Dietrich et al. 1988; Holland et al. 1986). Therefore, based on our results, it is reasonable to suggest that the human subcortical locomotor circuitry is also capable of adaptive plasticity, just as in lower animals.

What is intriguing in our results is the relationship between the incidence of after-effects and age. Infants older than 9 months of age were much more likely to show after-effects than infants younger than 8 months (Fig. 5-4). We have demonstrated that methodological factors are highly unlikely to have accounted for these differences (see above). Thus, we are left with the possibility that maturation of the nervous system, or experience with stepping facilitates this form of learning. Previous exposure to similar repetitive perturbations is extremely unlikely because none of the infants could walk independently at the time of the experiment. Infants older than 10 months, however, are more likely to be able to walk around furniture and be exposed to situations where tripping could occur. Whether this experience affects the learning reported here remains unknown.

The maturation of certain neural pathways may also be essential for this type of learning. Although animal studies have shown that the cerebrum is not required for this type of learning (Edgerton et al. 2001; Hodgson et al. 1994; Lou and Bloedel, 1987), the specific brainstem or spinal pathways involved in this type of learning have not been identified. Some studies suggested that the cerebellum is important for motor learning during perturbed locomotion (Earhart et al. 2002; Yanigihara and Kondo, 1996). In contrast, Bloedel et al. (1991) found that the decerebrate animals could still learn to adapt their walking to trip-inducing stimuli 2 months to 1 year after a cerebellectomy. While this finding shows that the cerebellum is not absolutely essential for adaptation to repeated trip-inducing stimuli, it does not rule out the possible involvement of the cerebellum in intact animals. As infants approach 1 year of age, many neural structures are maturing, including the cerebrum, the corticospinal tract and the lateral cerebellar hemispheres (Barkovich et al. 1988; Brody et al. 1987; Kinney et al. 1988; Yakovlev and Lecours, 1967). It is possible that the maturation of these structures contribute to the learning effects reported here. Moreover, we do not know whether there are other maturational changes occurring in the spinal cord, for that might be important. So, while it is clear there are age related changes in an infant's ability to demonstrate this form of learning, we cannot address the cause for these changes in our study.

In an earlier study from this laboratory, Lam et al. (2003) used a different protocol to determine if learning occurred in young infants. In that study, infants stepped with a small weight attached to the lower leg. When the weight was suddenly removed, some infants demonstrated an after-effect (i.e. high stepping) immediately upon removal of the weight.

The primary difference in the findings between the present study and the previous one is that the learning did not seem to be dependent on the age of the infant in the earlier study. We feel that this difference is likely related to the protocol of the experiments. When the weight was attached to the infant, the infant had a choice of whether or not to respond to the weight (i.e., he/she could compensate by using more flexor activity, or not respond and drag his/her foot more). This option may have resulted in greater variability in the learning exhibited, because those who chose not to respond would not be expected to show an after-effect. In this study, the infants had no choice but to respond to the disturbance, because stumbling-corrective responses are a form of reflex. Thus, all infants responded, and indeed responded in a similar way. The current protocol, therefore, is much more robust at showing learning if it was present.

5.4.4 Comparison with other species

The after-effect observed in this study was relatively short-lived, lasting only 2-4 step cycles. In contrast, the after-effects reported in the decerebrate ferrets/cats were much longer (more than 25 step cycles in some cases) (Bloedel et al. 1991; Lou and Bloedel, 1987). The difference in experimental protocol may account for the difference in results. More step cycles (more than 25 in some cases) were perturbed in their experiment (Bloedel et al. 1991; Lou and Bloedel, 1987) whereas we were limited to six. Technically, it was very difficult to apply many consecutive perturbations in human infants. Their stepping is more variable than human adults and their tolerance to stepping on the treadmill is also very limited.

The duration of stimulation is known to have an impact on the duration of the response as demonstrated in experiments studying other types of learning (reviewed in Kandel, 1977; Wolpaw and Tennissen, 2001). For example, while brief series of electrical stimulation of sensory fibers produce potentiation of spinal reflex lasting for seconds, longer period of stimulation produces a much longer period of potentiation which could last for minutes or hours (Lloyd, 1949, Spencer and April, 1970). The after-effects last longer for subjects who are exposed to a longer period of walking on a rotating disk (Weber et al., 1998). The much higher number of perturbed step cycles may be one of the reasons why longer after-effects were seen in decerebrate ferrets and cats than in human infants.

Our results are more similar to those reported by Edgerton et al. (2001). They reported that the maximum swing height remained higher than the control value for 2-5 step cycles following 10 trip-inducing stimuli. It is unclear whether the shorter-lasting after-effects in spinal cats compared to the decerebrate ferrets/cats are due to the difference in experimental protocol (i.e. number of perturbed step cycles) or a difference in preparation (i.e. decerebrate versus spinal). Further experiments are required to further investigate these issues.

In summary, many infants close to the age of 9 months or older can learn to adapt to trip-inducing stimuli by altering the motor program to accommodate changes in the locomotor environment, just as in lower animals. The results thus suggest that the locomotor circuitry in humans is capable of adaptive plasticity, before the onset of independent walking. Infants younger than 9 months of age were much less likely to exhibit this form of learning. Future studies could focus on the reason for this effect of age.

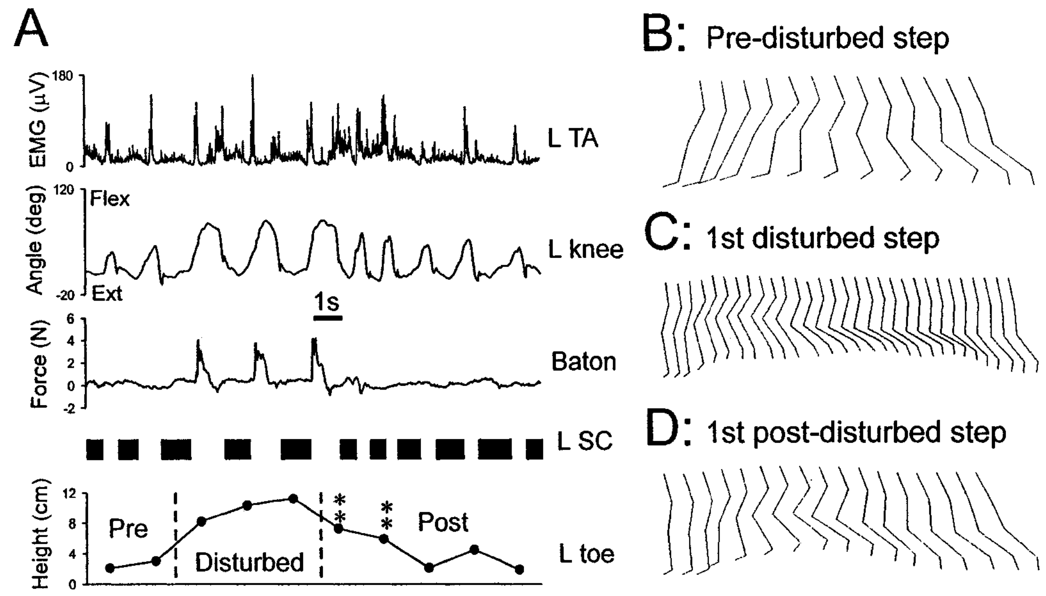

Figure 5-1. Single subject data showing an after-effect

A. Data from subject AAP: Signals from the left TA EMG (1st trace), left knee goniometer (2nd trace), instrumental baton (3rd trace) are shown. The left step cycle (SC) is illustrated in the 4th trace. The black bars represent the stance phase whereas the spaces between the bars represent the swing phase. The bottom trace indicates the maximum toe clearance for the pre-disturbed steps (pre), disturbed steps (demarcated by vertical dashed lines) and 5 post-disturbed steps (post). Each data point represents one single step. In this particular example, three consecutive swing phases were disturbed. High stepping persisted for another 2 step cycles before the maximum toe height returned to control value [statistical tests (z-score) were only performed for the post-disturbed steps; single asterisk: $p<0.05$, double asterisk: $p<0.01$]. **B-D.** Stick diagrams for the normal step immediately before the first disturbance (pre-disturbed step) **(B)**, the first disturbed step **(C)** and the first post-disturbed step **(D)**. The infant reacted to the disturbance by generating a high step **(C)**. Immediately following the removal of the trip-inducing stimuli, the infant continued to demonstrate high stepping, indicating the presence of an after-effect **(D)**.

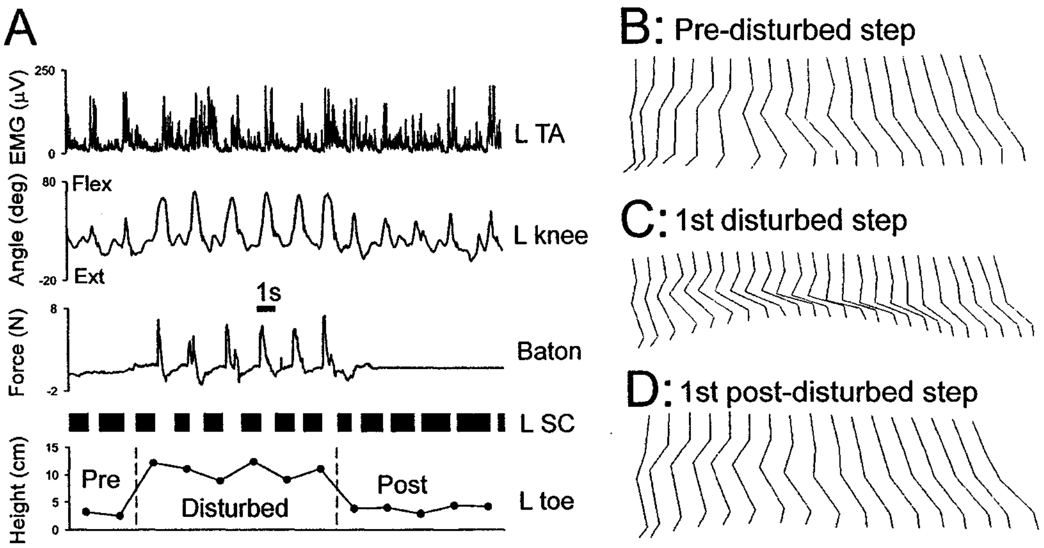

Figure 5-2. Single subject data showing no after-effect
A. Data from subject KIB: The figure convention is the same as Figure 5-1. Six consecutive swing phases were disturbed. However, the maximum toe height immediately returned to control value following the removal of the stimuli. **B-D.** The infant reacted to the trip-inducing stimuli by generating a high step **(C)**, similar to the example in Figure 1. However, the limb trajectory for the first post-disturbed step **(D)** resembled that for the pre-disturbed step **(B)**, indicating the absence of an after-effect.

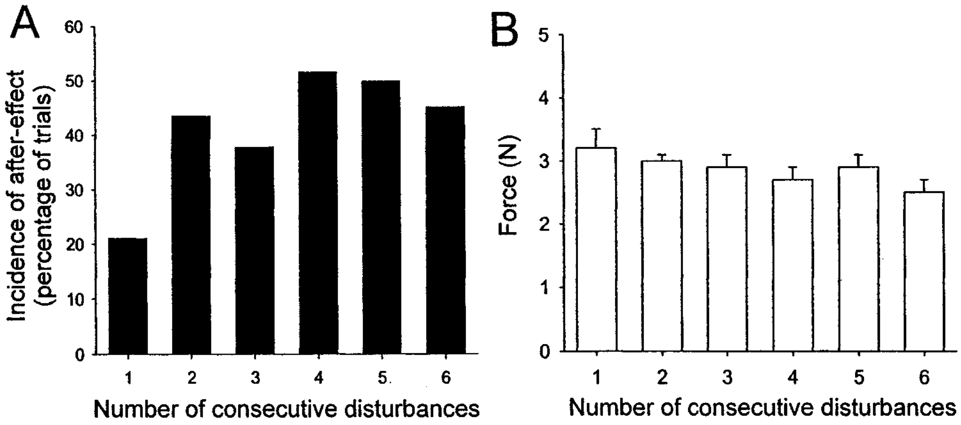

Figure 5-3. Incidence of after-effect and the number of perturbed step cycles

A. The percentage of trials with an after-effect was relatively low when a single step cycle was perturbed. When 2 or more consecutive swing phases were disturbed, the incidence of after-effect was increased.

B. There was no significant difference in force regardless of the number of consecutive disturbances applied. The error bar indicates one standard error.

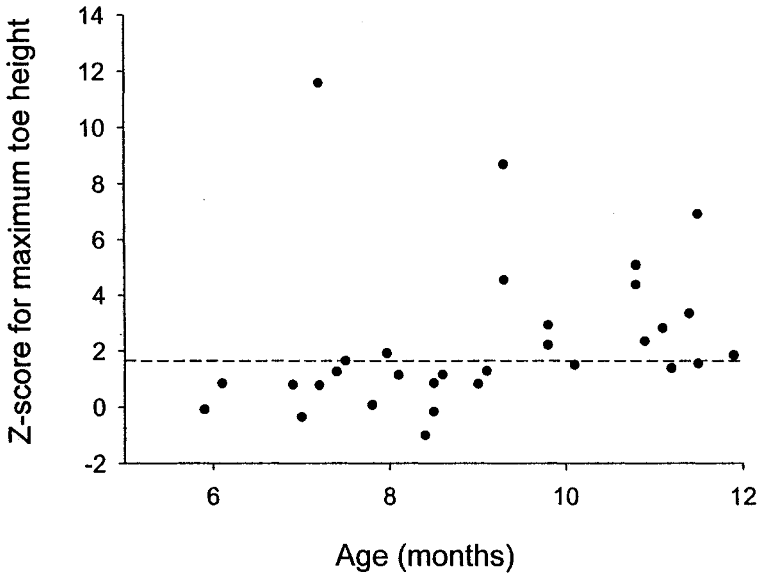

Figure 5-4. Distribution of z-score for maximum toe height
The horizontal axis represents age while the vertical axis represents the z-score for maximum toe height. Each data point indicates the average z-score for one subject. A score greater than 1.645 (indicated by the horizontal dashed line) indicates a significant difference in maximum toe height between the first post-disturbed step and the averaged control step. It is apparent that older infants (>9 months) tend to show a higher z-score than the younger infants.

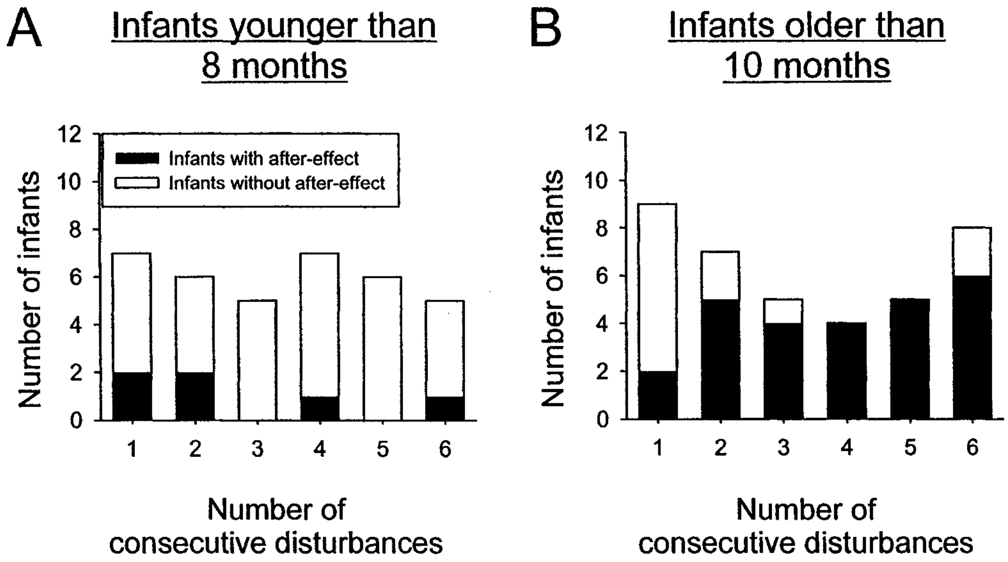

Figure 5-5. Relationship between age and incidence of after-effect

The infants were divided into two groups: those younger than 8 months (**A**), and those older than 10 months (**B**). The open bars indicate the infants without an after-effect whereas the solid bars indicate the number of infant who demonstrated an after-effect. After-effect tended to occur more often in older infants, especially when the number of the perturbed step cycles was more than two.

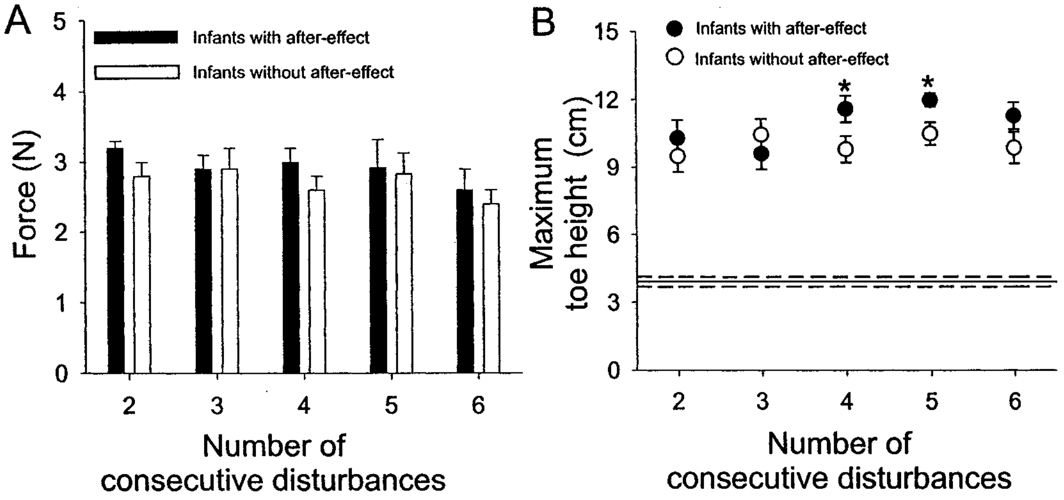

Figure 5-6. Force applied and maximum toe height during the disturbed steps
A. Force applied during the disturbed steps. The solid bars represent those infants with an after-effect whereas the open bars represent those without an after-effect. There was no significant difference in force between the two groups of infants regardless of the number of consecutive disturbances. **B.** Maximum toe height during the disturbed steps. The solid circles represent those infants with an after-effect whereas the open circles represent those without an after-effect. The solid line and the dashed lines represent the averaged control value and one standard error, respectively. The two groups of infants responded to the disturbances similarly.

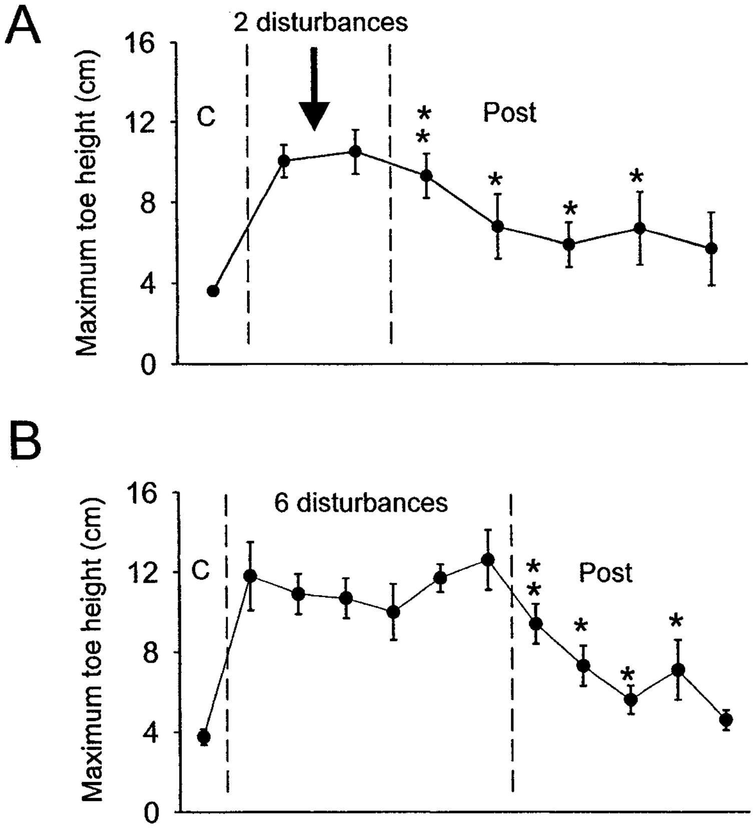

Figure 5-7. Time course of after-effect

A. Data from the infants who showed an after-effect following 2 consecutive disturbances are shown (N = 10). Each data point represents a single step averaged across the subjects. The control step (C), disturbed steps (demarcated by the vertical dashed lines) and post-disturbed steps (post) are shown. The trip-inducing stimuli clearly caused an increase in maximum toe height during the swing phase. The maximum toe height remained above the control value for another 4 steps (single asterisk: $p<0.05$, double asterisks: $p<0.01$). **B.** Data from the infants who showed an after-effect following 6 consecutive disturbances (N = 7). The maximum toe height remained above the control value for another 4 steps after the withdrawal of the disturbances.

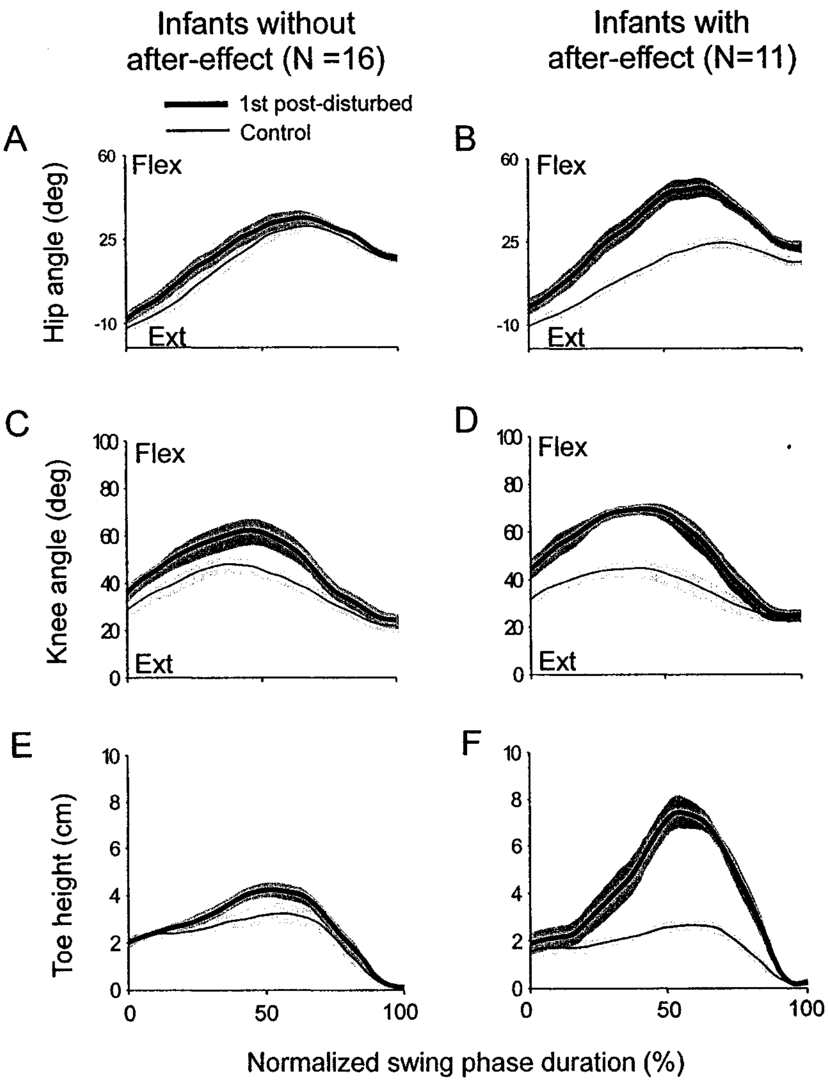

Figure 5-8. Kinematic changes associated with an after-effect
The left panel **(A-C)** shows the data for those infants who did not show an after-effect while the right panel **(D-F)** shows the data for those who showed an after-effect. The changes of hip angle **(A, D)**, knee angle **(B, E)** and toe height **(C, F)** are plotted against the time during the normalized swing phase (0% represents toe off; 100% represents toe contact). In each diagram, the thin solid line indicates the control step (with the light gray shade representing one standard error). The thick solid line represents the first post-disturbed step (with the dark gray shade representing one standard error). For the infants who did not show an after-effect, the hip and knee motion as well as toe trajectory for the first post-disturbed step only showed minor changes compared with the control steps. In contrast, for the infants who demonstrated an after-effect, there was a large increase in hip and knee flexion, accompanied by an increase in toe clearance for the first post-disturbed step.

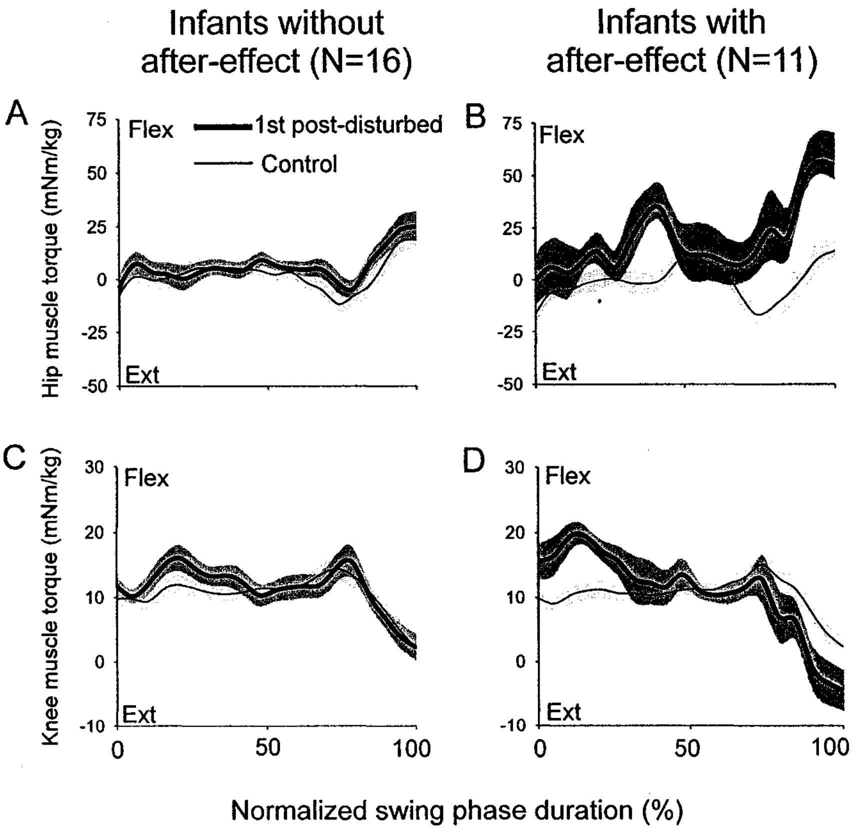

Figure 5-9. Hip and knee muscle torque profiles
The left panel **(A & B)** shows the data for those infants who did not show an after-effect while the right panel **(C & D)** shows the data for those who showed an after-effect. The average hip **(A & C)** and knee **(B & D)** torque profiles are illustrated. The figure convention is the same as Figure 5-8. For the infants who showed an after-effect, there was a significant increase in knee flexor torque followed by an increase in hip flexor torque in the early part of the swing phase.

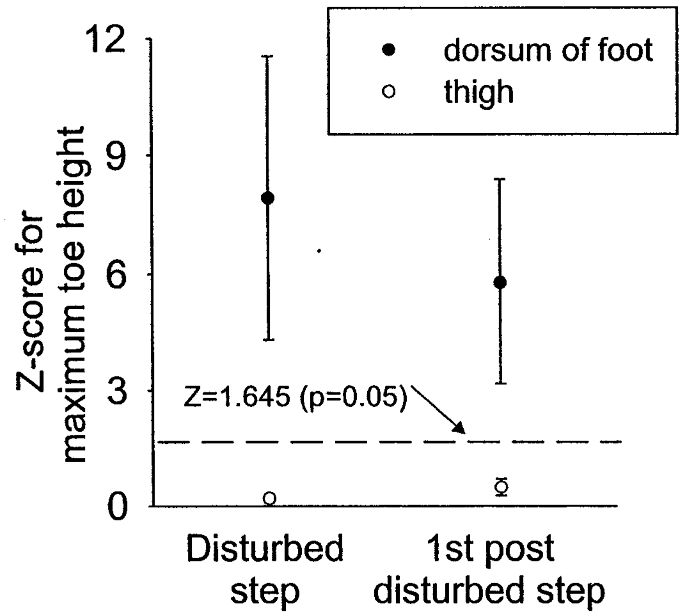

Figure 5-10. Control experiments
Average z-score for maximum toe height for the disturbed and first post-disturbed steps. The black dots represent the results from foot stimulation whereas the open dots represent those from thigh stimulation. Only the data from the four infants who showed an after-effect following stimulation to the foot were included (i.e. z score>1.645). None of these infants showed an after-effect following stimulation to the thigh.

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CHAPTER 6 - GENERAL CONCLUSION

6.1 Summary

The locomotor pattern in lower animals is highly adaptable to transient perturbations or long term alterations in the locomotor environment. It reflects both the powerful influence of sensory input on the locomotor pattern and the tremendous flexibility of the locomotor generator. Sensory control of locomotion has been extensively studied in lower animals. Does the locomotor control in humans bear resemblance to that in lower animals such as cats? Or is there a fundamental difference between the species? The knowledge gained from animal work alone cannot answer these questions. Human experiments must be done. Studying the stepping behavior of the infants allowed us to gain insight into the behavior of the human locomotor CPG before the cerebrum exerts full control. The projects in this thesis examined several important issues regarding sensory control of locomotion in human infants.

One of the new findings of this thesis is that sensory control of human locomotion is strikingly similar to that in cats (reviewed in Orlovsky et al. 1999). First, it was shown that similar sensory signals are important in controlling the timing of the phase transition in both cats and human infants (Chapter 2). Hip position and load are important factors to determine the timing of the stance to swing phase transition in human infants, just as in cats. Moreover, I have quantified the inverse relationship between hip position and load, which shows that the two factors are interdependent in controlling the timing of the transition from stance to swing phase. This information is not yet available from animal work. Second, the two legs are extremely coordinated so that ground support is maintained despite various forms of perturbations (Chapter 3), just as in cats (Forssberg et al. 1980b; Gorassini et al. 1994; Grillner and Rossignol, 1978; Hiebert et al. 1996; Matsukawa et al. 1982). Finally, the thesis showed that the subcortical locomotor circuitry in human infants is capable of adaptive locomotor plasticity, just as in cats. Specifically, Chapter 5 showed that subcortical locomotor circuitry in human infants can learn. The locomotor pattern adapts to sustained changes in the locomotor environment, such as the presence of an obstacle. The spinal circuitry in cats also can learn following exposure to different sensory experience (Bouyer et al. 1998, 2001; De Leon et al. 1998; Edgerton et al. 2001; Hodgson et al. 1994).

This thesis also highlights the subtle difference in locomotor control between humans (bipeds) and cats (quadrupeds). Although both human infants and cats showed well coordinated bilateral responses to perturbations during walking (Forssberg et al. 1977, 1980b; Gorassini et al. 1994; Hiebert et al. 1994; Halbertsma, 1983; Kulagin and Shik, 1970), it was found that the incidence of in-phase stepping triggered by various types of disturbances was relatively low when compared to chronic spinal cats (Chapter 3) (Grillner and Rossignol, 1978). In bipeds, only one leg is supporting the weight of the body when the other leg is in the swing phase. In response to perturbations during walking, it is thus more critical for bipeds than quadrupeds to quickly re-establish ground support to prevent a fall.

Another new finding of this thesis is that we put forward a conceptual model of sensory gating during walking, which is derived from the results in Chapter 4. The locomotor CPG in cats and other lower animals is capable of selectively gating sensory inputs (reviewed in Orlovsky et al. 1999; Pearson, 1993). Now we found that the human infant locomotor circuitry is capable of doing the same. However, no model has been proposed to explain the control of sensory inflow as the direction of walking changes. In Chapter 4, we proposed a new conceptual model of sensory gating for the initiation of the swing phase during different directions of stepping in infants. Depending on the direction of walking, the most powerful input to trigger the swing phase changes. Moreover, we proposed that the gains of transmission of different reflex pathways form a continuum, which corresponds to the smooth transitions between the infinite number of directions of walking. Such sensory gating allows for reflex responses appropriate for the behavioral state of the subject (reviewed in Pearson, 1993).

Overall, this thesis showed striking similarities between the behavior of the human locomotor generating networks and that of the lower animals in response to sensory inputs. In the human infant, different aspects of sensory control of locomotion, such as the control of the timing of the phase transitions, the coordination of limb movements, the gating of sensory input and the adaptability of the locomotor pattern, all bear resemblance to those in cats.

6.2 Future directions

6.2.1 General direction

The findings from this thesis helped us gain important insight into the behavior of the human locomotor CPG. However, the limitation of studying infants is that we often cannot explore further into the neural mechanisms underlying the behavior. Therefore, having gained the knowledge of the behavior of the human CPG, animal work can then be done to study in more detail the neural mechanisms that help explain the behavior observed.

One of the significant findings in this thesis is that the subcortical locomotor circuitry in human infants can learn. The issues of locomotor plasticity, training and learning are some of the most fascinating and interesting aspects of locomotor control. Further study in this area can have important contributions to developing rehabilitation techniques for neurological patients who have decreased walking ability. The specific research ideas are discussed in the following sections.

6.2.2 Sensory control of stance to swing transition

Chapter 2 showed that there is an interaction between hip position and load. If load gets higher, the hip angle required for the initiation of the swing phase becomes increasingly more extended. Previous animal work has indicated that such interaction may also be present in the cats. Hiebert et al. (1996) found that stretching the iliopsoas muscle by the same amount when the leg was immobilized produced a greater reduction of the period of extensor activity than that produced during quadrupedal walking. The difference could be due to the increase in force-feedback generated in the leg during quadrupedal locomotion, which promotes extensor activity. Based on unpublished observations, increasing the force in ankle extensors through mechanical or electrical means also reduced the effects of the flexor muscle afferents on the locomotor rhythm (Hiebert et al. 1996). However, the relationship between the force-sensitive afferents in extensors and the stretch-sensitive afferents in flexors has never been quantified.

One of the limitations of studying human infants is that the role of specific afferent systems in controlling the stance to swing transition cannot be addressed. First, many afferent systems could have been activated by the disturbances. Second, the disturbances were all applied manually, which is more variable. Therefore, it was technically unfeasible to further quantify the interaction between hip position and load. Animal experiments could be done in the future to evaluate quantitatively the interaction between specific afferent classes in different muscle groups. The results from these experiments would hopefully give us a better understanding of how the two systems combine to control the stance to swing transition.

6.2.3 Interlimb coordination

The results in Chapter 3 clearly showed that the two limbs are extremely coordinated despite the application of various forms of disturbances. The initiation of the swing phase on one side is usually accompanied by the stance phase on the other side. In-phase stepping is rarely triggered by the disturbances employed in the study. Does the human infant maintain such alternating stepping pattern with more extreme forms of disturbances? When cats are placed on a split-belt treadmill, with the two belts running at very different speeds, bilateral adjustments occurred so that 1:1 rhythm was maintained (Forssberg et al. 1980b; Halbertsma, 1983; Kulagin and Shik, 1970). Similar adaptation occurred in adult humans in spite of a four-fold difference in speed between the two sides (Dietz et al. 1994). Could infants show such interlimb coordination if placed on a split-belt treadmill? Thelen et al. (1987) showed that 7-month-old infants were able to modify their step cycle to maintain interlimb coordination. However, the speeds used were very slow and the difference between the two sides was only two-fold (0.1 and 0.2m/s). A few questions remain unanswered. Could infants maintain interlimb coordination if the speed difference is increased to four-fold or more, just as in the adults? Could younger infants (less than 7 months) show such adaptation? Experiments can be done in the near future to investigate these issues.

6.2.4 Sensory gating

The results in Chapter 4 showed that the sensory inputs signaling hip position/ motion are selectively gated depending on the direction of walking. In particular, while hip extension is the most powerful input to initiate the swing phase during forward walking, hip adduction and abduction become the most potent sensory input to trigger the initiation of the swing phase during sideways walking in the leading and trailing limb, respectively. But what muscle afferents are responsible for the initiation of the swing phase in other directions of walking? This issue could be examined in more detail by conducting animal studies. If the gains of transmission of reflex pathways from the hip abductors or adductors are reduced during forward walking, stimulating the afferents from hip adductors and adductors should have minimal effect on the locomotor rhythm. If there is a way to induce sideways walking in cats, the same stimulation can be applied to these muscles and observe whether there is a difference in response. The same concept can also be applied to backward walking. The hip is flexed when the swing phase is initiated during backward walking (stretch of hip extensors). What are the effects of stimulating the stretch-sensitive afferents in different hip muscle groups during backward walking?

Previous animal and human work has shown that phase-dependent responses of cutaneous reflex are different when the direction of walking was switched from forward to backward (Buford and Smith, 1993; Duysens et al. 1996). Duysens et al. (1996) proposed that the change in the pattern of reflex modulation could be explained by a motor program working in reverse. However, humans are able to walk in infinite number of directions with smooth transitions in between. Based on the results in Chapter 4, we proposed a model in which the gains of transmission of different reflex pathways also form a continuum. Human experiments can be conducted to determine the pattern of reflex modulation as the subject slowly changes the direction of walking from forward to backward. It would be interesting to find out whether the modulation pattern also shows a gradual change.

6.2.5 Adaptation to sustained changes in sensory input

The results in Chapter 5 showed that the locomotor pattern can adapt to long term changes in sensory input. Following repeated trip-inducing stimuli, some infants continued to generate high steps despite the absence of the stimulus. However, many questions remain unanswered. First, the after-effect obtained was quite short-lived as reported in Chapter 5. In most cases, the high stepping persisted for about 2 - 4 steps after the removal of the stimulus. No clear relationship between the number of disturbances and the number of high steps was identified. Could the after-effects last longer if more consecutive disturbances were applied? Second, some infants did not show an after-effect despite up to 6 consecutive trip-inducing stimuli were applied. Would these infants have shown an after-effect if we had applied more disturbances? Third, if the infants require a large number of disturbances to induce an after-effect on the first day of experiment, would it take fewer number of disturbances to induce the same effect when they return the next day? Finally, the location of the adaptive plasticity is unknown. The results in Chapter 5 indicated that older infants showed a higher incidence of after-effect following repeated trip-inducing stimuli. The learning effect may be related to the maturation of certain neural pathways. Decerebrate ferrets demonstrated high stepping following repeated trip-inducing stimuli, indicating that this form of learning does not necessarily involve the cerebral cortex (Lou and Bloedel, 1987). It has also been found that the acquisition of this stepping behavior does not require an intact cerebellum because decerebrate-decerebellate ferrets also demonstrate high stepping following repeated trip-inducing stimuli (Bloedel et al. 1991). Similar but weaker adaptive response has also been reported in spinal cats (Edgerton et al. 2001; Hodgson et al. 1994). However, no group data were presented and details were lacking in their reports. Whether spinal cats in general show this adaptive response thus still remains as a question. It would be worthwhile to repeat these experiments in different preparations of the cat in order to find out what structures in the nervous system are important for this type of learning.

Human experiments showed that adults are capable of adapting to split-belt locomotion (Dietz et al. 1994; Jensen et al. 1998; Prokop et al. 1995). Generally, it took about 12 - 15 strides for the subjects to adapt. With repeated trials, the subjects could quickly adapt within the first 3 strides, indicating the presence of learning (Prokop et al. 1995). Would infants be able to learn in a similar way? Another issue concerns the after-effects seen after a period of split-belt locomotion. After a period of walking on a split-belt treadmill, a difference in speed [(0.85 kilometers per hour (km/h)] between the two legs persisted although the perceived speed was equal between the two sides (Jensen et al. 1998). Would such adaptational effects occur in infants, well before the onset of independent walking? It would be interesting to determine whether infants continue to show asymmetrical stepping following a period of walking on a split-belt treadmill (i.e. after-effect). Again, the length of time spent on walking on the split-belt treadmill and the time course of the after-effect could be examined in more detail.

Another related issue is the transfer of learning. Prokop et al. (1995) showed that the learning effect did not occur when the slow and fast sides were switched. The subjects took about the same amount of time to adapt to the "mirror" condition. Does similar phenomenon occur in infants? On the other hand, Earhart et al. (2001) showed that following a period of walking on a rotating disk, the locomotor trajectories of forward and backward walking were very similar, indicating a transfer of learning between different directions of walking. Similarly, after a period of walking forward on a split-belt treadmill, would after-effects be present in both forward and backward walking?

Adaptive plasticity of the locomotor circuitry is one of the issues addressed in Chapter 5. The locomotor pattern is highly modifiable by experience. It has been shown that practice increases the incidence of stepping (Yang et al. 1998). Could the locomotor pattern be modified by different forms of practice? It has been shown in spinal cats that the walking ability is highly dependent upon the type of training. Those cats that received treadmill training could walk for a longer period of time and at a higher speed than those that received training in standing (De Leon et al. 1998; Edgerton et al. 1992). Different types of training also have a major impact on the locomotor pattern. For example, spinalized infant rabbits were trained on a motor-driven bicycle, which could move the limbs in an alternating pattern or in a synchronous pattern (Viala et al. 1986). It was found that those rabbits trained in the alternating pattern developed an alternating stepping pattern while those trained in the synchronous pattern tended to maintain in-phase stepping (Viala et al. 1986). These studies provide compelling evidence that the locomotor adaptive plasticity could be induced by specific patterns of sensory input given during training. Could infants show such adaptive plasticity following different types of training? For example, would the stepping pattern be different if the infant is trained to jump (synchronous pattern) rather than the normal alternating pattern?

In summary, this thesis has attempted to explore how sensory information influences the locomotor generator in the human infant. It also highlights some of the similarities and differences between the behavior of the human spinal and brainstem locomotor circuitry and that of the lower animals. However, many questions remain unanswered regarding the operation of the human locomotor generator. Further research can provide us with additional insight into how the nervous system controls walking in humans, which may have important implications for developing effective treatment strategies for improving walking in patients with neurological disorders.

6.3 References

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