Chapter 6.3

Corticospinal Control of Human Walking

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Human walking has four main gait characteristics: (1) humans walk erect on two legs, (2) at the moment of contact with the ground the leg is almost fully extended, (3) the foot strikes the ground heel first (plantigrade gait), and (4) during the late swing phase, the body's center of gravity (COG) is outside the base of support. By contrast, the COG of bipedal walking robots, such as Mark Tilden's Robosapien and Honda's more complex Asimo, is always within the base of support. As a consequence of the straight legged nature of human gait, there is a mixed activation of extensor and flexor muscles at heel contact and the activities of the various leg extensors are not in phase. Ankle extensor activity is delayed, occurring after heel contact when activity in most other leg extensors has ceased (Capaday, 2002). In other mammals, such as cats, the activities of leg extensors are in phase when the foot makes contact with the ground, digits first (digitigrade gait). Alexander (1992) suggested that the straight-legged characteristic of human walking minimizes muscular activity by using the legs like struts. Birds walk on two legs, but in a squatted position. Penguins walk with a more erect posture than other birds, but they still walk in a squatted position and, like other birds, walk on their toes. Thus, with the exception of a similar gait adopted occasionally by some monkeys and apes, an erect, bipedal, plantigrade gait pattern is unique to humans and its neural control needs to be understood on its own terms (Capaday, 2002). Here I review in a critical manner studies on the role of the motor cortex (MCx) during human walking and some aspects of spinal reflex mechanisms as they relate to MCx control.

It may seem surprising to suggest a role for the MCx in a seemingly automatic task such as walking, but there are good reasons for this. The MCx not only issues voluntary motor commands, but it also mediates reflex-like responses to stretch of upper limb muscles (Matthews et al., 1990; Capaday et al., 1991) and integrated responses such as contact placing (Amassian et al., 1979). Its importance increases with phylogenetic order, as judged from the motor deficits that result from lesions of the corticospinal tract (CST) (Passingham

et al., 1983). For example, damage to the MCx disrupts swallowing, a seemingly automatic and unconscious task (Hamdy and Rothwell, 1998). Likewise, damage to the MCx or CST results in severe walking deficits in humans and macaques, the most conspicuous being foot drop (e.g., Knutsson and Richards, 1979; Jagiella and Sung, 1989; Nathan, 1994; Courtine et al., 2005). Moreover, locomotor recovery of persons with incomplete spinal cord injury (SCI) is associated with improved corticospinal transmission assessed with transcranial magnetic stimulation (TMS) methods (Thomas and Gorassini, 2005). However, it is not clear from these clinical observations what aspect(s) of walking the MCx controls. Nor does a parallel improvement of corticospinal transmission and locomotion necessarily prove that the MCx has a direct role in controlling human walking. It may simply be that other descending tracts recover with a similar time course. This also applies to ascending, or sensory tracts. Human walking requires critical coordination of the upper body (head, arms and trunk (HAT)), with leg movements. Spinal lesions interrupt sensory inflow from the legs to supraspinal centers involved in balancing the HAT, depriving these centers of the required feedback.

In the cat, evidence from single-unit MCx recordings, intracortical microstimulation and deficits following lesions of ascending and descending spinal cord tracts, suggests that the MCx may be involved in the transition from the stance to swing phases of the step cycle (Armstrong and Drew, 1984a, 1984b; Jiang and Drew, 1996; Rho et al., 1999). However, no single observation directly proves this. For example, the peak firing rate of different MCx neurons occurs at widely different times during the step cycle (Armstrong and Drew, 1984a, 1984b). Additionally, sensory inputs may also modulate the firing rate of MCx neurons, making interpretation of their activity ambiguous. What is clear is that the MCx can initiate voluntary corrective adjustments, such as stepping over a suddenly-appearing obstacle (Drew, 1988). In a major series of studies on methods to restore walking deficits after a spinal cord lesion in rats, it was shown that behavioral therapies which encourage supraspinally-mediated movements result in a cortex-dependent recovery of locomotor capacity (van den Brand et al., 2012). Strong evidence was provided for MCx involvement in initiating and sustaining locomotion, as well as in corrective movements. However, in rodents the MCx is not essential for locomotion (Courtine et al., 2007). Thus, the results of van den Brand et al. (2012) show that the MCx can affect control actions normally mediated by other neural systems, a finding of potential clinical value. Let us now consider studies on the role of the MCx during human walking.

6.3.1 FORWARD WALKING

In a study that tackled this directly, the MCx leg area was activated by TMS at various phases of the step cycle (Capaday et al., 1999). Input–output curves of motor-evoked potentials (MEPs) in the ankle extensor soleus and the ankle flexor tibialis anterior (TA) were measured (Devanne et al., 1997). TMS during the stance phase elicited MEPs in both muscles. In 4 of 6 subjects, TA MEPs were larger than those of soleus throughout stance. This is surprising, since soleus is active during the stance phase, but the TA remains active only at the onset of stance. In contrast, TA MEPs were not elicited when soleus was activated voluntarily. Additionally, soleus MEPs were reduced by ∼30% during the stance phase compared to those during voluntary contractions at matched background electromyographic (EMG) levels. No comparable reduction of TA MEPs was observed. Finally, TMS of the MCx at various phases of the step cycle did not alter the timing of the next step, indicating that the MCx was not part of the neural system controlling the timing of step cycles, nor did it have access to putative spinal timing circuits. It was concluded that during locomotion, the corticospinal system taken as a whole (MCx circuitry and spinal relays of the corticospinal pathway) affects spinal circuits controlling the ankle flexor TA more than those controlling the ankle extensor soleus, but during voluntary contractions requiring attention, it affects both equally (Capaday et al., 1999).

It had been suggested that TA MEPs are enhanced at the transition from stance to swing (Schubert et al., 1997) but this was not seen in the Capaday et al. study (Capaday et al., 1999), though at the onset of a voluntary reaction time (RT) task, TA MEPs do increase substantially, prior to any measurable change in background EMG (Schneider et al., 2004; Davey et al., 1998; MacKinnon and Rothwell, 2000). It was suggested that MEPs may depend more on α-motoneuron activity than on activity in MCx (Schneider et al., 2004), which has important methodological implications to be discussed below.

In another study, subthreshold TMS of MCx was found to suppress muscle activity during walking (Petersen et al., 2001). It was proposed that this was due to intracortical inhibition, and that the result supported the idea that MCx was directly involved in activating both TA and soleus (Petersen et al., 2001). However, subthreshold TMS of MCx only suppresses voluntarily-generated EMG activity in about 10% of trials and the effect is weak. It is therefore not a reliable indicator of the proposed involvement of MCx. More importantly, H-reflexes elicited at the time of maximal reduction of voluntary soleus EMG activity by sub-threshold TMS are reduced relative to control H-reflexes (Fig. 6.3.1). This suggests that TMS that is subthreshold for activating α-motoneurons activates spinal interneurons, possibly Ia-interneurons which inhibit α-motoneurons. The important point is that the inhibition is at the spinal rather than at the cortical level.

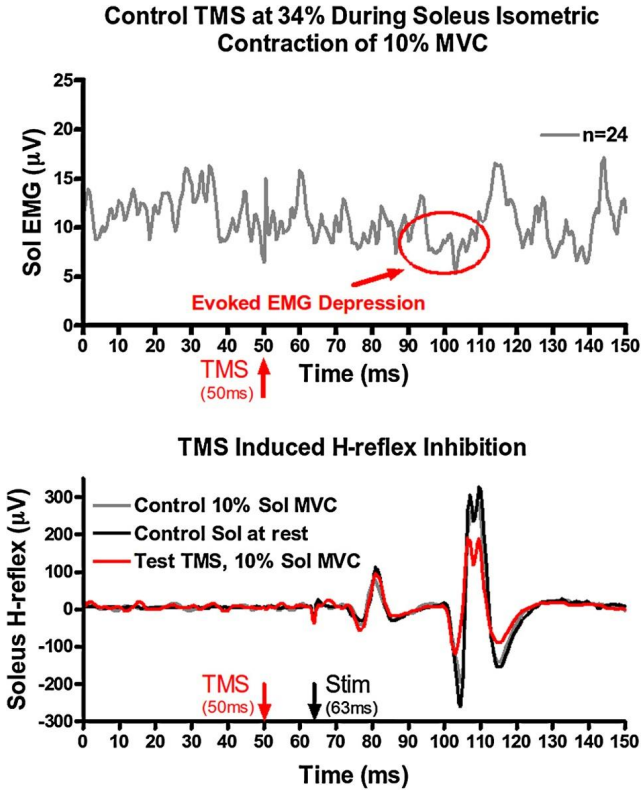

FIGURE 6.3.1 A single subthreshold TMS pulse produces a small depression, or inhibition, of the ongoing EMG. When the H-reflex is timed to arrive at the time of maximal inhibition it is markedly reduced compared to its value at rest. This shows that the cortical stimulus evokes inhibition in the spinal cord.

6.3.2 BACKWARD WALKING

Lacquaniti et al. (1999) proposed that backward walking is controlled at the kinematic level by the time-reversed motor program of forward walking (Lacquaniti et al., 1999). Interestingly, the modulation pattern of the soleus H-reflex is not a time-reversed version of the pattern during forward walking. In forward walking, the soleus H-reflex increases progressively during the stance phase nearly in parallel with soleus EMG levels (Capaday and Stein, 1986; Crenna and Frigo, 1987; Ethier et al., 2003). It is abruptly reduced just before swing and remains essentially shut off throughout the swing phase and early stance while TA is active (Ethier et al., 2003). The modulation pattern of the H-reflex during forward walking thus follows the classic pattern of reciprocal inhibition between antagonistic muscles (Lavoie et al., 1997). But when untrained

subjects walked backward on a treadmill the modulation pattern was very different. There was a marked increase of the soleus H-reflex in mid-swing, well before soleus EMG activity started and toe contact occurred (Schneider et al., 2000). It was suggested that this was associated with reduced confidence due to uncertainties of balance and timing of toe contact. In support of this idea, when subjects held onto handrails, the high-amplitude H-reflex in mid-swing was no longer present (Schneider and Capaday, 2003). This was also the case after ten days of training without handrail support. During the training period the maximal H-reflex shifted progressively from mid-swing to early stance, suggesting that the reflex activity was anticipatory and gradually declined as subjects gained confidence. The reflex changes were not due to changes in ankle muscle activity or leg kinematics, indicating that they were adaptations in the motor program controlling backward walking.

Because backward walking on a treadmill appears to require greater conscious control, it seemed reasonable to ask whether the MCx might be involved. Specifically, it was posited that in untrained subjects, CST activity during mid-swing depolarizes soleus α-motoneurons subliminally and thus brings them closer to threshold, explaining the unexpectedly high amplitude H-reflex (Ung et al., 2005). To test this hypothesis, TMS was applied to the leg area of the MCx during backward walking. MEPs were recorded from soleus and TA in untrained subjects at different phases of the step cycle. It was reasoned that if soleus MEPs could be elicited in mid-swing while soleus was inactive, this would be strong evidence for increased postsynaptic excitability of soleus α-motoneurons. In the event, despite the presence of an unexpectedly large H-reflex in mid-swing, no soleus MEPs were observed at that time. Rather, they were in phase with soleus EMG activity (Fig. 6.3.2). During backward walking soleus MEPs increased less rapidly as a function of voluntary EMG activity than they did in voluntary contractions. Furthermore, a conditioning stimulus to the MCx facilitated the soleus H-reflex at rest and during voluntary plantarflexion, but not in the mid-swing phase of backward walking. As mentioned above, with daily training, the maximal H-reflex shifted progressively from mid-swing to early stance, and its amplitude was considerably reduced compared with its value on the first day. By contrast, no changes were observed in the timing or amplitude of soleus MEPs with training (Fig. 6.3.2).

Taken together, these observations make it unlikely that the MCx is involved in the control of the H-reflex during the backward step cycle of untrained subjects, nor in its progressive adaptation with training. Instead, the large amplitude of the H-reflex in untrained subjects in backward walking, and its adaptation with training, may be due to control of presynaptic inhibition of Ia-afferents by other descending tracts.

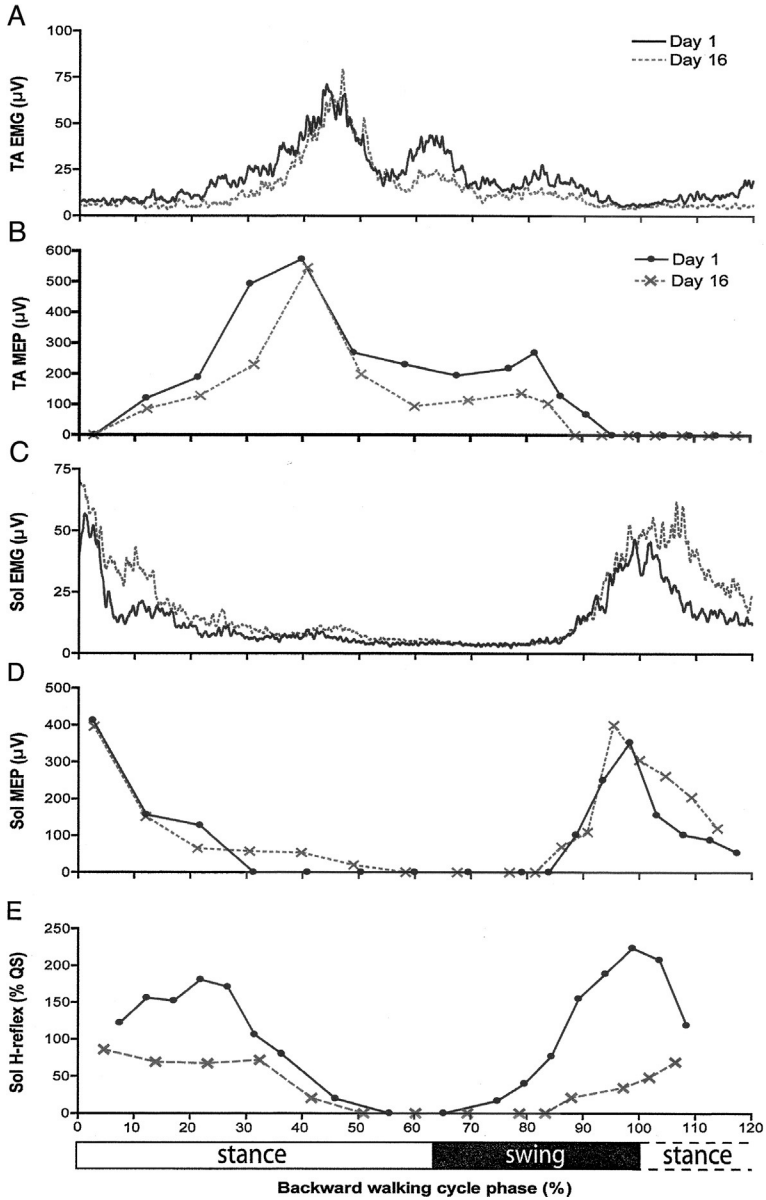

FIGURE 6.3.2 Comparisons of soleus H-reflex and MEP modulation patterns during backward walking on day 1 and day 16 of training. On day 1, the soleus H-reflex began to increase in the mid-swing phase prior to soleus EMG onset, whereas the soleus MEP increased at soleus EMG onset. At day 16, the soleus H-reflex had decreased throughout the step cycle, most markedly in mid-swing and early stance. In contrast, there was little difference between soleus and TA MEPs on days 1 and 16.

6.3.3 COMMENTS ON THE ROLE OF MOTOR CORTEX IN FORWARD AND BACKWARD WALKING

Let us first consider the detailed study of Courtine et al. (2005) on the effects of unilateral transections at the thoracic level of the CST in macaques (Courtine et al., 2005). A week after transection the animals regained some stepping capacity, with notable leg drag. However, the monkeys were unsuccessful at retrieving an item with the affected hindlimb. Thus a group of muscles could be activated during locomotion, but not voluntarily. Some 12 weeks later the spatial and temporal characteristics of the kinematics and EMG activation patterns during walking returned to near control values and yet the ability of the animals to retrieve an item with the affected hindlimb remained significantly impaired. Clearly, the CST lesion had a differential effect on stepping and voluntary activation of the affected hindlimb. If the MCx were directly and equally involved in the two tasks, one would expect that muscles activated in one task would also be equally activated in the other. After spinal cord injury, Sherrington (1947) noted "*In the monkey and in man spinal shock is not only peculiarly intense but peculiarly long lasting*" (Sherrington, 1947). The mechanisms of spinal shock are poorly understood, but we know that many spinal neurons, including interneurons, undergo what Sherrington termed "*isolation dystrophy*", they degenerate and die. We also know that many different central and peripheral inputs converge on common interneurons. Furthermore, studies on fictive locomotion in cats have shown that pattern generating and reflex circuits may be intertwined (McCrea, 2001). Thus, gait deficits after CST lesions may be the result of interneuronal dysfunctions, as well as other yet unknown mechanisms. Put simply, the effects of CST lesions do not necessarily reveal the function of the CST per se. The same logic applies to hemiplegic gait after a stroke; the resulting gait deficits do not necessarily prove that cortical systems drive human walking.

Let us now consider the TMS studies. No facilitation of TA MEPs was found at the transition from stance to swing, by contrast to the large facilitation observed some 12 ms before the onset of voluntary TA EMG activity. It may be argued that at the transition from stance to swing, TA α-motoneurons are repolarizing from a state of hyperpolarization and that this is different from a voluntary dorsiflexion, where the α-motoneurons may be either at a resting membrane potential, or even subliminally depolarized. However, at or very near the onset of activity these considerations do not apply in either case. It therefore seems unlikely that the human MCx is involved in either triggering or driving flexor muscle activity during walking. During backward walking, whilst a prominent soleus H-reflex can be elicited in mid-swing, it is not possible to evoke an MEP in soleus, or to facilitate the H-reflex with MCx TMS. Thus two principal observations argue against the direct involvement of the MCx during

either forward or backward walking. Regarding the enhanced TA MEPs during the stance phase of walking, in this phase the flexion reflex is enhanced relative to that during standing. Additionally, it is significantly enhanced during swing relative to voluntary leg and ankle flexion at matched levels of EMG activity. Presumably therefore, TMS of the MCx during walking activates interneurons in the spinal circuit mediating the flexion reflex which are in a greater excitable state.

The last point that requires explanation is the apparent reduction of CST input to soleus α-motoneurons during the stance phase of gait. As discussed in Subchapter 6.4, a significant portion of ankle extensor muscle activity may be due to inputs from muscle spindle and tendon organ afferents, mediated in part by spinal interneurons. CST inputs to these interneurons may be partially occluded by the afferent input. Another possibility is that the enhanced excitability of the flexion reflex network inhibits interneurons that transmit part of the CST input to soleus α-motoneurons. This issue requires further investigation.

6.3.4 CONCLUSIONS ON CORTICOSPINAL CONTROL

The human MCx may well act to voluntarily initiate or stop walking (Jiang et al., 2015). However, the locomotor drive is likely to be mediated by brainstem nuclei that have been shown in numerous studies to be capable of initiating and sustaining locomotion (e.g., Steeves and Jordan, 1980; Noga et al., 1991; Cowley et al., 2008. Damage to the MCx would then lead to impairments in the initiation of gait and also of voluntary gait modifications, such as changing direction. These effects must be distinguished from direct phasic drive of locomotor muscles once walking has started. On balance, the evidence presented above does not support the notion that the MCx is involved in this direct control. In stating this I do not claim that the MCx has no role in controlling walking that is in progress. Perhaps it is involved in balancing the HAT and along with other descending systems, in maintaining excitability and balance within brainstem and spinal circuits. The present conclusions are based on noninvasive neurophysiological experiments. They stand to be corrected by more probing methods that may be developed in the future. Finally, human walking involves more than just placing one foot after the other on the ground. The body must remain balanced and for most of the time it is balanced on only one leg. This is the main difficulty of human walking and it requires the integrative action of many ascending and descending neural systems.

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