Do human bipeds use quadrupedal coordination?

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Tackling the question of whether control of human gait is based on that of a quadrupedal locomotion system is of basic and practical relevance. During evolution, the increased influence of a direct cortical–motoneuronal system in parallel with more specialized hand function might have replaced phylogenetically older systems that organized locomotor movements. However, recent research indicates that interlimb coordination during human locomotion is organized in a similar way to that in the cat. Hence, it is hypothesized that during locomotion, corticospinal excitation of upper limb motoneurons is mediated indirectly, via propriospinal neurons in the cervical spinal cord. This allows a task-dependent neuronal linkage of cervical and thoraco–lumbar propriospinal circuits controlling leg and arm movements during human locomotor activities. The persistence of such movement control has consequences for rehabilitation and the applicability of animal research to human patients with spinal cord injury.

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The coordination of forelimb and hindlimb rhythmic activities is a main characteristic feature of quadrupedal locomotion [1]. Specialized neural circuits located in the caudal spinal cord [the so-called central pattern generator (CPG) for locomotion] organize hindlimb locomotor activity, whereas specialized circuits in the rostral spinal cord control forelimb movements [2,3]. The coordination of both circuits is mediated by propriospinal neurons with long axons, which couple the cervical and lumbar enlargements of the spinal cord [4,5].

In many respects, bipedal and quadrupedal locomotion share common spinal neuronal control mechanisms. As in quadrupeds, long projecting propriospinal neurons couple the cervical and lumbar enlargements in humans [6]. Furthermore, the coordination of limb movements during walking is similar in human infants [7–8], adults [9,10] and quadrupeds [2,11]. Nevertheless, there are also distinct differences because the upper limb in primates has become specialized to perform skilled hand movements. The evolution of upright stance and gait, in association with a differentiation of hand movements, represents a basic requirement for human cultural development [12].

This review deals with the question of whether there is a task-dependent switch, from a strong direct (i.e. monosynaptic) cortical–motoneuronal control during reaching [13] and skilled hand and finger movements [14] to a more indirect control by cervical propriospinal circuits during locomotion. This indirect control appears to occur in the cat [15]. Evidence will be presented for the hypotheses that (1) the neuronal control of human locomotor activities is based on the coordination of the quadruped fore- and hindlimbs and (2) this phylogenetically older system coexists with the newly developed, direct cortical–motoneuronal control of skilled hand movements.

Interlimb coordination

Lower limbs

The regulation of human walking requires a close coordination of muscle activation between the two legs. Perturbation of gait, for example by short obstruction of the swing phase, evokes a bilateral response pattern [16]. This organization of human interlimb coordination has at least three similarities with that of cats.

First, according to the short latencies of the electromyographic (EMG) responses [16], human interlimb coordination is thought to be mediated at a spinal level, as in the cat [17]. A contribution from the cerebellum to this spinal interlimb coordination via reticulospinal neurons has been suggested for both cats [18] and humans [19].

Second, during stepping on a split-belt treadmill with the belts running at different speeds, the legs act in a cooperative manner in human infants [20] and adults [21–23], each limb affecting the time–space behaviour of the other. In line with studies on spinalized cats [2], this indicates that the spinal cord contains networks responsible for each limb and that these can be interconnected in a flexible manner. In general, initiation of the swing phase on one side is contingent on the contralateral limb being in the stance phase, in both human adults [9,10] and infants [7,8,24]. Thus, there is an innate capacity of the neuronal circuitry that controls walking. Such a pattern of interlimb coordination has also been reported for a variety of preparations in the cat [17,25,26] and agrees with the 'half-centre' model proposed for organization within the spinal cord of neuronal circuits that can generate locomotor movements (i.e. the CPG) [27,28]. In this model, the neuronal circuits that coordinate the leg flexor activity of both sides during the swing phase of locomotion (i.e. the flexor half-centres) mutually inhibit one another. By contrast, the extensor half-centres on each side have no mutual inhibitory connections, agreeing with the coexistence of the stance phase on the two sides.

Third, the spinal neuronal control of walking and its similarities with quadrupedal locomotion are also

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reflected in the modulation of cutaneous reflexes evoked in the lower limbs. A task-dependency of cutaneous reflexes has been shown in standing versus running [29,30] and cycling versus static [31] contraction. Cutaneous reflex responses in leg muscles are sensitive to the specific motor task that is being performed [32,33]. Furthermore, a nerve specificity of cutaneous reflex modulation exists, which seems to be functionally important [34–36]. It has been suggested that certain features of this reflex modulation are determined by the CPG [3,31,37], as would parallel observations made in the cat [38,39].

Upper limbs

There is also interlimb coordination of the arms during a great variety of tasks, but only during rhythmic movements does this coordination seem to be organized in a similar way to that of the legs. For example, the modulation of cutaneous reflexes during rhythmic cyclical arm movements [40,41] corresponds to that of the legs [35] in respect to their task-dependency, nerve specificity and phase-dependency. This implicates similar control mechanisms in the reflex modulation of upper and lower limbs [41,42]. These observations are again in accordance with studies in the cat, in which the organization and pattern of cutaneous-reflex modulation were similar in the fore- and hindlimbs [39].

Coordination of arm and leg movements

There is some evidence that interlimb coordination is organized similarly in the lower and upper limbs during cyclic movements of humans and cats. This indicates that the neuronal coordination and patterns of reflex modulation are conserved within the human lumbar and cervical spinal cord. This could serve as a basis for the remaining piece of quadrupedal limb coordination during human bipedal walking, the similarity of coordination of upper and lower limb muscles in humans and that of fore- and hindlimbs in quadrupeds (cf. Ref. [43]).

Evidence for neuronal coupling

Recent experiments have indicated that there is neuronal coupling of upper and lower limb muscles during various human locomotor activities [44]. A linkage between the cervical and lumbar enlargement of the spinal cord by propriospinal neuronal circuits with long axons can also be inferred on the basis of H-reflex studies [45,46] (in this technique, monosynaptic spinal-reflex excitability is tested by electrical stimulation of group Ia afferents). For example, during rhythmic movements of one foot, a cyclic H-reflex modulation was observed in the upper limbs [46]. According to recent studies using functional magnetic resonance imaging [47], the supplementary motor area might be involved in the supraspinal control of this coupling between upper and lower limb movements.

Task-dependency of neuronal coupling

Only during walking do mechanical impulses applied to one leg (in the middle or at the end of the stance phase) evoke distinct bilateral arm EMG responses. These were larger in the deltoid and triceps muscles than in biceps brachii, and were modulated within the stance phase [48].

Similar interlimb reflex responses in arm muscles were also obtained following electrical stimulation (above motor threshold) of the distal tibial nerve (a mixed nerve, which innervates plantar foot muscles and the skin of the sole) during walking [48]. Correspondingly, arm muscle responses were absent when stimuli were applied during either standing with voluntary arm swing or sitting while writing (i.e. with a comparable background EMG activity) (Fig. 1). These observations indicate a flexible task-dependent neuronal coupling between upper and lower limbs. The pathway that couples upper- and lower-limb movements seems to become gated by the activity of the CPG during walking. It has been concluded that a stimulus applied to a leg can exert a direct influence not only on the compensatory leg muscle EMG activity but also, depending on task, on the neuronal control of upper-arm muscles of both sides [48]. The range of movements in which such task-dependent neuronal coupling of upper- and lower-limb movements occurs has yet to be determined. The stronger impact of leg flexors in interlimb coordination is in line with the increasing evidence that leg flexor and leg extensor muscles are differentially controlled, both in animals [49] and humans [5,50–52] (reviewed in Ref. [9]).

Interlimb coupling in spinal cord injury

Further evidence for neuronal coupling between upper and lower limbs comes from studies in patients with cervical spinal cord injury. So-called 'interlimb reflex responses' can be evoked with short latency in distal muscles of upper limbs by electrical stimulation of the tibial nerve at the ankle [53]. These reflex connections might reflect a loss of supraspinal inhibition or, alternatively, a sprouting of ascending propriospinal systems occupying synaptic locations vacated by degenerating descending connections. Functional and anatomical evidence indicates that plasticity of neuronal circuits exists caudal to the level of the spinal cord lesion [54] and that the plasticity can be potentiated by training and experimental manipulations [55,56].

Furthermore, it has been shown that the more rostral the spinal cord lesion, the more 'normal' the locomotor pattern induced in patients with complete paraplegia or tetraplegia [57]. This observation indicates that neuronal circuits underlying locomotor 'pattern generation' in humans are not restricted to any specific level of the spinal cord but rather, that an intricate neuronal network contributing to bipedal locomotion extends from thoraco–lumbar to cervical levels [57]. Such organization is in line with that of

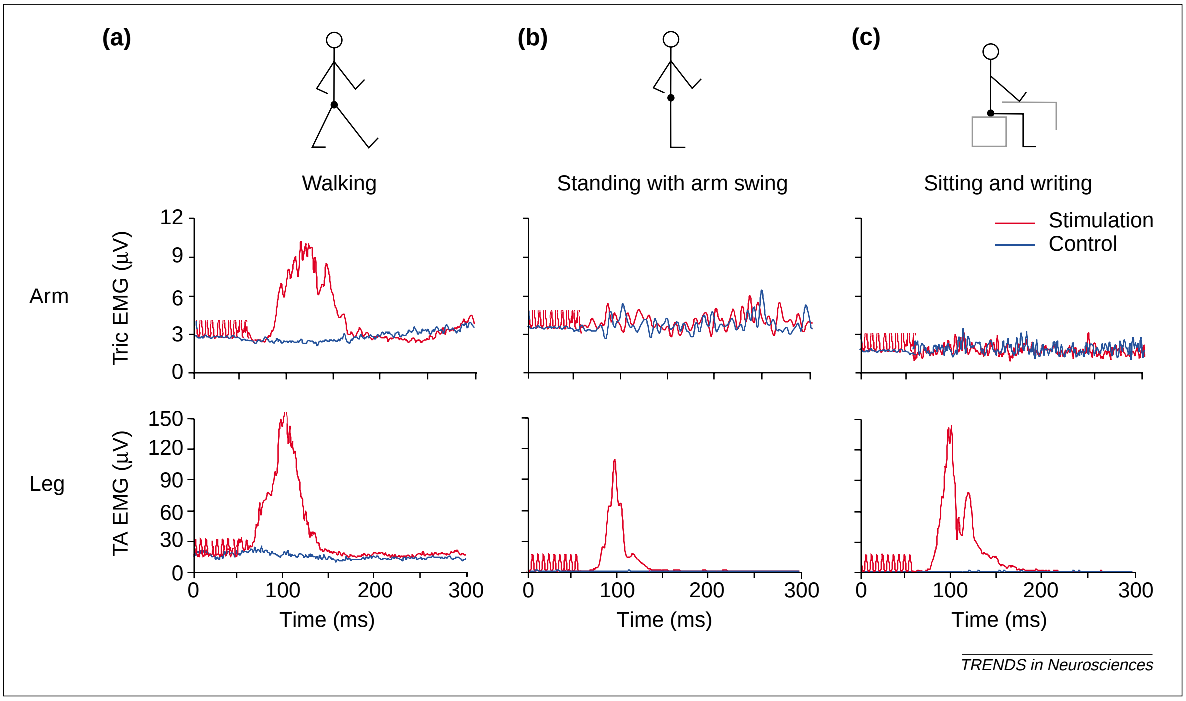

Fig. 1. Interlimb reflexes: a comparison of walking, standing and sitting. Rectified and averaged right tibialis anterior (TA) and left triceps brachii (Tric) electromyographic (EMG) responses to a train of electrical stimuli applied to the right distal tibial nerve during walking (a; n = 100), standing with voluntary arm swing (b; n = 20) and sitting while writing (c; n = 20) (red). The data were obtained from a single subject. Control EMG recordings without stimulation (blue) are displayed for comparison. During walking, stimulation of the right tibial nerve was followed by leg and arm muscle EMG responses. However, arm muscle responses were absent when stimuli were applied during standing and sitting. This suggests that proximal arm muscle responses are associated with swinging of the arm during walking as a residual function of quadrupedal locomotion. Note the different calibration of the leg and arm muscle EMG. Stimulus artifacts are present on the left side of each graph. Adapted from Ref. [45].

quadrupedal locomotion, which requires coordination between neuronal circuits at cervical and lumbosacral levels, with the brainstem being the next highest coordinating centre [58]. However, it should be pointed out that, in primates, corticospinal drive is of greater importance to generation and maintenance of locomotor movements than it is in cats or rats [59].

Functional evidence

Recently it has been shown that arm and leg muscle activity is well coordinated during walking, crawling 'on all fours' or swimming [44]. In such conditions, arm and leg movements are locked with a fixed frequency relationship. Even if the leg movements are slowed by flippers, or if the mechanical interactions between the limbs are minimized (as in 'swimming' or 'crawling' in the air), this coordination is preserved [44]. This indicates a coupling of the neuronal circuits controlling arm and leg movements, which is again under supraspinal control. The frequency relationship characterizing this coordination corresponds to that observed in well-defined biological systems consisting of coupled oscillators [60].

Also during gait, swinging of the arms serves to regulate the rotation of the body (i.e. it counteracts torsion-related movements of the trunk) [61]. Therefore, swinging of the arms can be seen as an integral part of the dynamics of progression.

Differential control of upper-limb movements

The task-dependency of the neuronal coupling between upper and lower limbs might be based on a differential neuronal control of upper limbs during skilled hand movements and during locomotion. Direct cortical–motoneuronal connections to hand muscles are thought to determine the degree of dexterity in humans and non-human primates [62,63] (reviewed in Ref. [14]). It has been suggested that these phylogenetically new components are integrated into pre-existing neuronal circuits [64].

As a result of recent studies, there has been speculation that the greater influence of the direct cortical–motoneuronal system that parallels increased dexterity is accompanied by a decline in, or even loss of, the indirect transmission of corticospinal excitation by propriospinal neurons in the upper cervical spinal cord (C3–C4) [62,65]. The strong direct cortical–motoneuronal input from the cortex enhances the possibility of selective activation of hand muscles during skilled voluntary hand movements (Fig. 2a).

However, indirect evidence obtained by different experimental approaches indicates, that propriospinal neuronal circuits corresponding to those described for cats [66] persist, and most likely remain involved in the control of arm movement [67,68] (reviewed in Ref. [69]). It seems possible that there is an indirect corticospinal pathway to upper-limb motoneuron pools, in addition to the well-documented direct cortical–motoneuronal

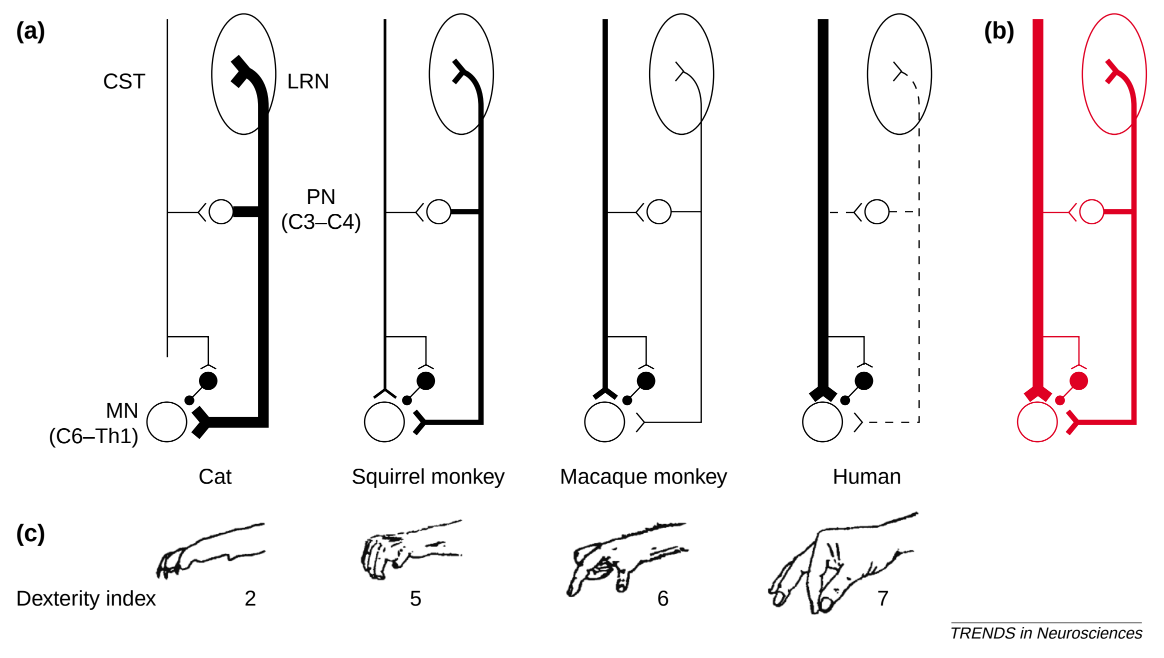

Fig. 2. Contribution of propriospinal and cortical–motoneuronal excitation to control of upper limb motoneurons in cat, squirrel monkey, macaque monkey and human. (a) Schematic diagram of the presumed propriospinal and corticospinal inputs to upper limb motoneurons in different species (adapted from Ref. [62]). According to this speculative view, the propriospinal neuronal system becomes progressively weaker from cat, through squirrel monkey, to macaque monkey. This change is accompanied by a progressive increase in the strength of the cortical–motoneuronal connection, which is stronger again in humans. It has been suggested by extrapolation of these changes that the propriospinal neuronal system is unlikely to play a major role in transmitting corticospinal excitation in humans (dashed lines). (b) According to the evidence presented in this review, the propriospinal neuronal system persists in humans for locomotor-like movements, despite the strong cortical–motoneuronal connections (c) Indices of dexterity for the four species [77]. Abbreviations: CST, corticospinal tract; LRN, lateral reticular nucleus; PN, propriospinal neurons; MN, motoneurons.

pathway [70]. Nevertheless, the data so far presented do not yet allow definitive conclusions to be drawn about direct and indirect cortical–motoneuronal connections and their function in humans.

On the basis of the available evidence, the following hypothesis is put forward and should be tested in the future (Fig. 2b). Efficient corticospinal excitation of upper-limb motoneurons via propriospinal neurons might occur during automatically performed movements, such as locomotion. By contrast, during skilled hand movements, strong cortical–motoneuronal input dominates and transmission through the propriospinal system becomes suppressed [67] – this might explain why stimulating the pyramidal tract or the motor cortex fails to demonstrate the indirect corticospinal projection in the macaque monkeys [65,71] or humans [72]. Such an interaction would be expected if propriospinal neurons in primates are under a stronger inhibitory control than those in cats [73].

Nevertheless, at present there is neither positive evidence for a release of this inhibition during purposeful tasks, such as locomotion, nor an indication of whether such a mechanism is also involved in other functional movements, such as throwing or reaching. Furthermore, there might be other ways of coupling the cervical and lumbar neuronal circuits, for example by direct corticospinal projections.

Practical consequences

Three practical consequences emerge from the observations indicating that basic neuronal control mechanisms underlying cyclical movements remain preserved during evolution. First, knowledge gained about the effects of regenerating pathways on movement performance observed in the rat [54,74] can, at least in part, be transferred to humans. In fact, by comparing the outcome of spinal cord injury in rats and humans (using electrophysiological, imaging and functional measures), a comparable course and extent of recovery was found [75].

Second, as a consequence of a quadrupedal-like coordination of locomotion in humans, it emerges that patients with more rostral spinal cord lesions might benefit more from neuronal regeneration than those with more caudal spinal lesions. In more rostral lesions, the integrity of complex neuronal network underlying locomotion is obviously preserved and ‘only’ a gain regulation is required.

Third, the demonstration of an interaction between cervical and thoraco–lumbar neuronal circuits in humans has relevance for the rehabilitation of patients with an incomplete spinal cord lesion. Involvement of arm movements in the training, corresponding to experiments in spinalized cats [76], might have a positive effect on the locomotor capacity in these patients.

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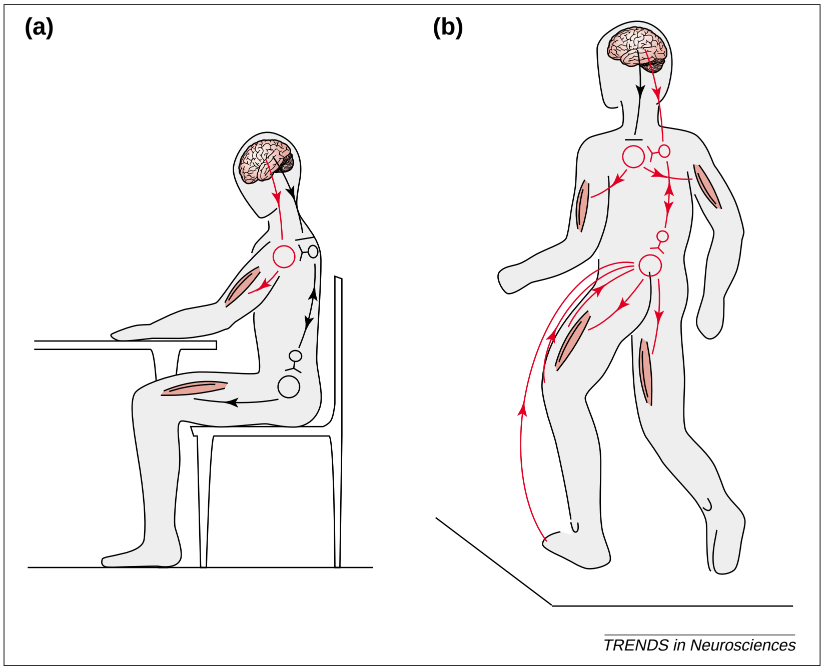

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Fig. 3. Movement control during different motor tasks. According to the research cited in this review, neuronal control of arm movement is task-dependent. (a) During skilled hand movements, strong direct cortical–motoneuronal excitation is predominant (red lines) and the cervical propriospinal neuronal system is inhibited. (b) During locomotion, it is assumed that the brain command is predominantly mediated by interneurons. Cervical and thoraco–lumbar propriospinal systems become coupled and coordinate arm and leg movements (red lines). The caudal part of (b) is adapted from Ref. [78].

Conclusions

It is proposed that a flexible coupling of thoraco–lumbar and cervical centres allows humans to use the upper limbs for manipulative and skilled movements or, alternatively, for locomotor tasks. This implicates a functional, task-dependent gating of neuronal pathways between the neuronal circuits controlling lower and upper limb muscles during walking, reflected in the arm swing as a residual function of quadrupedal locomotion (Fig. 3). This hypothesis is based mainly on five pieces of indirect evidence. First, interlimb coordination and reflex modulation are similarly organized during locomotion in humans and cats. Second, task-dependent coupling of upper- and lower-limb muscle occurs during walking, but is prevented during skilled hand movements. Third, in line with such a flexible coupling of cervical and lumbar interneuronal circuits, transmission through the indirect cortical–motoneuronal system seems to be inhibited during a precision hand task. Fourth, during rhythmic movements of a foot, H-reflex modulation also involves upper limbs. Finally, during locomotor activities such as swimming or crawling, there is a fixed coupling between upper and lower limb movements. Further studies are required to define more precisely the functions of evolutionarily older and evolutionarily newer neuronal control mechanisms in the broad variety of movements that can be carried out by humans.

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