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# Plasticity of connections underlying locomotor recovery after central and/or peripheral lesions in the adult mammals

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This review discusses some aspects of plasticity of connections after spinal injury in adult animal models as a basis for functional recovery of locomotion. After reviewing some pitfalls that must be avoided when claiming functional recovery and the importance of a conceptual framework for the control of locomotion, locomotor recovery after spinal lesions, mainly in cats, is summarized. It is concluded that recovery is partly due to plastic changes within the existing spinal locomotor networks. Locomotor training appears to change the excitability of simple reflex pathways as well as more complex circuitry. The spinal cord possesses an intrinsic capacity to adapt to lesions of central tracts or peripheral nerves but, as a rule, adaptation to lesions entails changes at *both* spinal and supraspinal levels. A brief summary of the spinal capacity of the rat, mouse and human to express spinal locomotor patterns is given, indicating that the concepts derived mainly from work in the cat extend to other adult mammals. It is hoped that some of the issues presented will help to evaluate how plasticity of existing connections may combine with and potentiate treatments designed to promote regeneration to optimize remaining motor functions.

**Keywords:** locomotion; pharmacology; spinal sections; plasticity; reflexes; training

## 1. INTRODUCTION

This review summarizes multiple observations related to the functional recovery of locomotion after spinal injury, especially in animal models and humans with spinal cord injuries, and discusses putative mechanisms of this recovery. Functional recovery of locomotion after central nervous system lesions in the adult suggests that the properties of circuits and cells normally implicated in the generation and control of locomotion have been modified to optimize its re-expression through a reduced circuitry. However, we are generally still far from establishing how new anatomical connections made by regenerating axons or sprouting from undamaged pathways or how plastic changes in the transmission within existing circuits correlate with functional recovery of locomotion. Nevertheless, it is worthwhile to report and discuss experiments demonstrating such recovery because some of the conclusions reached can be helpful in evaluating the recovery of function in paradigms aimed at fostering regeneration or axonal sprouting.

### (a) *Miraculous locomotor recoveries*

#### (i) *False resurrections versus miraculous functional locomotor recovery*

In an excellent paper addressing issues of anatomical regeneration (Steward *et al.* 2003), the authors provided several anatomical guidelines to distinguish, in spinal lesion studies, true regenerating axons from

spared axons. Indeed, there are several possible pitfalls to avoid before claiming that true regeneration has occurred. This is even more important since some of these pitfalls may obfuscate the claim of functional recovery in the same studies. As detailed later, the neural controls of locomotion are widely distributed and partial recovery of function does not necessarily imply regeneration or the acquisition of new function. Therefore, distinguishing recovery of function due to regeneration from the re-expression of partial remnant function is as important as differentiating true anatomical regeneration from sprouting.

#### (ii) *Preparations*

Choice of preparation is important when studying the recovery of locomotion. It is often argued that lesions best approximating clinical situations in humans should be studied in animals (i.e. contusion). While this argument is entirely valid when assessing potential therapeutic approaches to spinal lesion, it might blur the issue on the mechanisms of recovery themselves. Indeed, when studying the recovery of locomotion in the hindlimbs after a spinal lesion, it is crucial to be aware that the spinal cord caudal to the injury has autonomous intrinsic capabilities to generate locomotor movements, when sensory afferents are stimulated or pharmacological agents are applied. This will be detailed later for various species. Using complete surgical section of the cord might not be the most clinically relevant preparation but it is the only one that can clearly identify these intrinsic spinal capabilities that must be taken into account when claiming the return of function after partial spinal cord injuries.

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One contribution of 13 to a Theme Issue 'The regenerating brain'.

Although it is not always feasible to make a second spinal section to assess that the recovered function is dependent on regenerating or sprouting axons, it should be strongly encouraged. In some studies, such second complete spinal lesions were performed in spinal rats implanted with 5-hydroxytryptamine (5-HT; serotonin) cells below the transection to demonstrate that locomotor recovery was entirely due to spinal mechanisms and not potential re-growth of axons through the spinal lesion (Ribotta *et al.* 2000).

The level of the complete spinal section is important because some segments of the spinal cord are crucial for the expression of locomotion. In the rat, upper lumbar segments are important for locomotion either because they essentially contribute to pattern generation (Cazalets 2000; Bertrand & Cazalets 2003) or are more excitable and prone to generate locomotion when activated (Kjaerulff & Kiehn 1996). Similar findings in the cat indicate that midlumbar segments (L3–L4) have profound effects on locomotion since restricted chemical activation or inhibition of these segments induces or inhibits locomotion (Marcoux & Rossignol 2000). Furthermore, spinal cats cannot walk after a lesion at caudal L4, which remains rostral to the main hindlimb motor neuron pools (Langlet *et al.* 2005).

The notion that all spinal segments are not equivalent applies not only to the organization of cellular elements but also to the distribution of multiple transmitter receptors at different spinal levels. For example, 5-HT receptors of various subtypes are distributed non-uniformly along the thoraco-lumbar cord so that the presence or absence of locomotor response to drugs may entirely depend on the level of the cord accessible to the drugs (damaged or undamaged; Schmidt & Jordan 2000). This point was important in the earlier mentioned studies on 5-HT cell grafts in adult spinal rats (Gimenez y Ribotta *et al.* 2000) since only those grafts that re-innervated appropriate levels (namely L2 in the rat) induced locomotor recovery.

### (iii) Scales and other measurements

Various techniques can be used to assess the recovery of locomotion after lesion. In rats, the Basso, Beattie and Bresnahan (BBB) scale (Basso *et al.* 1995) evaluates several aspects of locomotion on a 22-point scale (including the 0 level) of open-field locomotion. Such a scale has obviously been very useful to screen animals with partial spinal lesions and correlate the recovery of function with the amount of spinal damage after spinal contusion utilizing mechanical devices or controlled weight drops (Basso *et al.* 1996; Young 2002). However, it is based on qualitative assessment and its linear scale does not account for the nonlinearity of locomotor recovery. Moreover, the lowest and highest scores are not necessarily used (the worst and the best performances), which may distort statistics (see, however, the correction suggested by the originators of this scale; Ferguson *et al.* 2004).

However, as detailed elsewhere (Antri *et al.* 2002, 2003), the BBB score is severely limited when dealing with animal models with complete spinal section. Indeed, after such complete section, there are no neural mechanisms for fore- and hindlimb coordination. This

means that on the BBB scale the maximum attainable score is 11 since this is the highest possible score without fore- and hindlimb coordination. However, in the absence of such coordination, the quality of locomotor movements produced by the spinal cord below the lesion still evidently improves. Thus, this amelioration cannot be reflected with the BBB scale. This led some researchers (Antri *et al.* 2002, 2003) to use a modified 23-point scale whereas scores above 11 reflect improvements in body weight support, plantar foot contact and left–right coordination of the hindlimb locomotor movements.

Another concern with the BBB scale is the reliance on visual observation for fore- and hindlimb coordination over 4–5 cycles. The definition of coordination for this scale is a one-to-one correspondence between steps of the fore- and hindlimbs. Two independent oscillators at the same frequency can be ‘coordinated’, although they are not coupled. Fore- and hindlimb oscillators, which have evolved biologically to operate at close frequencies because they are usually coupled, will oscillate at their natural frequency if allowed to oscillate independently of each other and may appear coupled even though they are not. Such apparent coordination is well exemplified by studies in the cat in which extensive but partial lesions of the cord were performed at the last thoracic segment (T13; Brustein & Rossignol 1998). In such animals, fore- and hindlimb coordination could be maintained for several cycles, but precise measurements indicated a gradual shift of one limb pair with the other since both walked at a slightly different mean frequency. A casual observation over 4–5 cycles would miss this. Similar findings were reported for stepping in spinal mice (Leblond *et al.* 2003).

Therefore, it is most advisable to use electromyographic (EMG) recordings and kinematic measurements (Bélanger *et al.* 1996; Brustein & Rossignol 1998; Ribotta *et al.* 2000; Merkle *et al.* 2001; Leblond *et al.* 2003) to better characterize changes observed over several cycles after different types of lesions and experimental manipulations designed to improve recovery of locomotion. These quantitative methods ensure, for instance, that real and not apparent interlimb coordination has been regained or the joint movement and muscle activation have been restored close to normal. Obviously, when skilled locomotor movement must be assessed other methods, as reviewed by others (Basso 2004; Fouad & Pearson 2004), should also be complementary.

### (b) Conceptual framework of locomotor control

The conceptual framework of the organization and control of locomotion is also a key to the interpretation of locomotor recovery after spinal lesion. It has been known for a long time (Sherrington 1910) that spinal animals have the potential to generate well-organized bilateral locomotor movements of the hindlimbs as reviewed elsewhere (Delcomyn 1980; Grillner 1981; Rossignol 1996; Rossignol *et al.* 1996; Rossignol *et al.* 2002). Although not much is yet known concerning neural elements of the spinal circuitry, we know for a fact that it can operate in isolation from supraspinal commands and afferent feedback. The latter has been

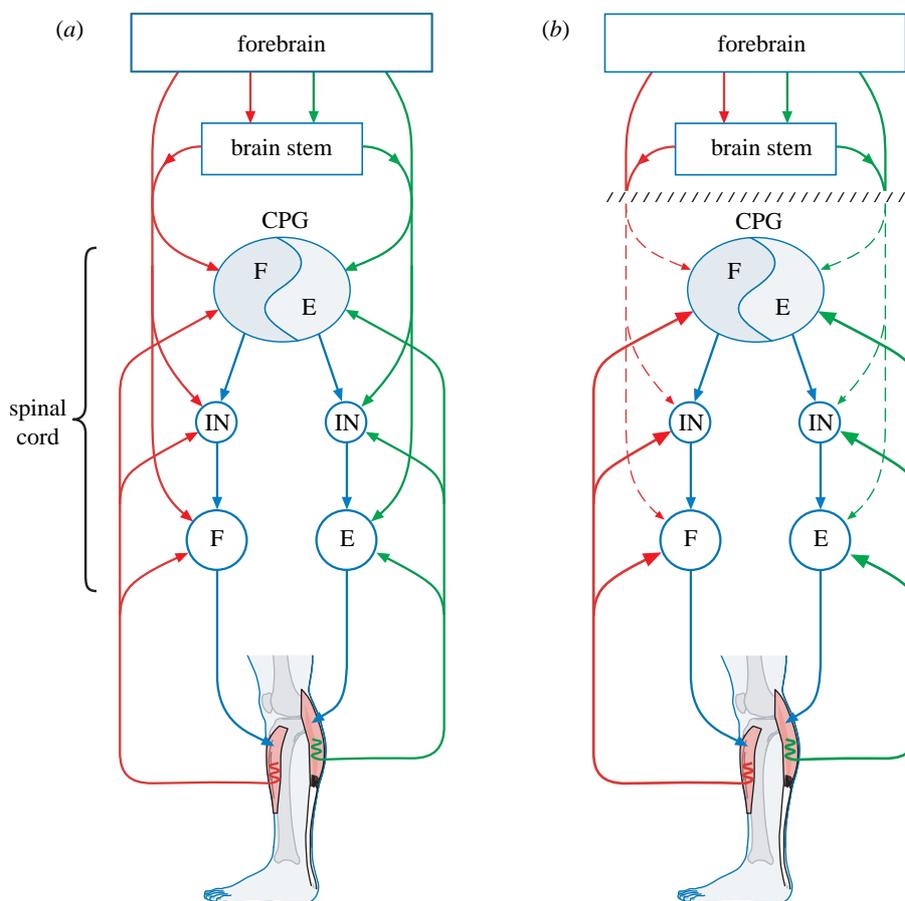


Figure 1. General scheme of the normal control of locomotion. (a) In this simplified scheme, essential elements of the control of locomotion are represented. At the core and within the spinal cord is a network of interneurons capable on its own to generate locomotion (central pattern generator, CPG). For the sake of simplification, the CPG has only two main phases: F (flexion) and E (extension). This CPG is presumed to project to groups of interneurons (IN), which in turn contact various pools of flexor (F) and extensor (E) motor neurons innervating flexor and extensor muscles, represented here in a human leg. Afferent feedback is represented generically by a single type of afferent originating from the muscles and should be interpreted to mean various proprioceptive afferents as well as cutaneous afferents. These afferents form intraspinal circuits (monosynaptic, disynaptic, trisynaptic and polysynaptic) that can reach the motor neurons, the interneurons or the CPG. Similarly, descending inputs from the forebrain or the brainstem can modify locomotion through actions on the motor neurons, interneurons or the CPG either directly or through the brainstem descending pathways. All these descending pathways are lumped for the sake of simplicity and include pathways with fast conduction (corticospinal, rubrospinal, reticulospinal and vestibulospinal) as well as slowly conducting and neurochemically defined pathways originating from the brainstem and releasing for instance noradrenaline or serotonin. (b) In this scheme, all the descending pathways are cut and degenerate (dashed lines). In this situation, the control of locomotion must rely on internal changes of connectivity within the spinal cord (not represented) and on an increased importance of sensory pathways from the periphery represented here as thicker lines that can reach the cord and influence locomotion by acting at several sites (motor neurons, interneurons or CPG).

elegantly demonstrated using ‘fictive locomotion’ in which spinal rhythms are recorded with peripheral nerve or ventral root discharges in the absence of any overt movement or phasic afferent inputs as a result of the curarization (Grillner & Zangger 1975, 1979). This is a key concept having far reaching consequences for the interpretation of animal paradigms to study locomotor recovery after spinal lesions (Grillner 2002). The concept of central pattern generation suggests that the basic locomotor pattern is generated within the spinal cord and that descending commands as well as sensory information interact with this circuitry to initiate, stop or modulate its characteristics (frequency, output amplitude and coordination; see figure 1a). This basic spinal circuitry is genetically determined since kittens spinalized prior to having actually walked develop walking capabilities of the hindlimbs (Grillner 1973; Forssberg *et al.* 1980a,b).

Therefore, locomotion is a genetically determined spinal circuitry with which afferent feedback and descending inputs interact. Thus, eliminating some afferent feedbacks (e.g. nerve sections, deafferentation) or sectioning descending pathways with surgical or mechanical methods removes inputs to the spinal locomotor generating circuits but does not affect the main spinal circuitry, which is normally involved in the generation of rhythmicity. After such lesions, however, a new equilibrium must be achieved between controllers to optimize the remaining locomotor capabilities. This reorganization suggests a great deal of plasticity in the connectivity of pathways controlling locomotor functions.

This sturdy but flexible design is important to ensure that locomotion, a basic essential function in animals, is optimized despite various types of central or peripheral nerve injuries that deprive it of some controls.

However, it raises the complexity for the experimenter wanting to show that a given treatment improves locomotor function after spinal cord injury (SCI). Indeed, what is due to the treatment and what results from spontaneous recovery of an intrinsic spinal function? The usual argument is that if control untreated animals do not show the same improvement then the latter is due to the treatment. With regeneration, this becomes problematic since partial regeneration of a given pathway might be accompanied by sprouting in undamaged pathways and the creation of new circuits that may reach spinal circuitry via reticulospinal, rubrospinal or propriospinal pathways (Raineteau *et al.* 2002; Steward *et al.* 2003; Bareyre *et al.* 2004) or even to neurochemically defined pathways that may change the overall excitability of the spinal circuitry. Therefore, the functional improvement resulting from a given treatment may in part be due to changes in undamaged pathways or the intrinsic spinal circuitry.

The latter point is important since amelioration of locomotion might not be due to a point-to-point reconnection between descending pathways and the spinal circuitry but rather to a generalized effect that may increase the overall excitability of the circuit. As will be seen later, intravenous, epidural or intrathecal injections of some neurotransmitter agonists can excite spinal locomotor circuits even in the absence of any descending connections. This is true even in chronic animals in which the terminals of aminergic descending pathways remaining below the lesion have disappeared. The implication here is that re-growth of descending pathways that can increase neurotransmitter release (e.g. 5-HT) can lead to some recovery of function even without a point-to-point re-growth of descending fibres with specific neural elements. Indeed, such neurotransmitter release could re-establish essential membrane properties crucial for rhythmicity. This constitutes the basis for studies using chronic drug administration to maintain or regain membrane properties involved in rhythm generation (Antri *et al.* 2002, 2003; Orsal *et al.* 2002).

It was felt necessary to address these general considerations in the introduction to better evaluate the experimental observations made in animal preparations and in humans with various types of spinal lesions. Because of the main theme of this review, more observations from animal experiments will be reported to highlight the plasticity of connections. In this context, the expression 'plasticity of connections' was taken to include changes in locomotor behaviour, modifications of reflexes or modulation of pharmacological responsiveness, which must implicate the plasticity of some connections.

## 2. FUNCTIONAL LOCOMOTOR RECOVERY AFTER SPINAL LESIONS

### (a) *Studies in animals*

#### (i) *Cat*

##### *Spontaneous recovery*

*Complete spinal section.* After a complete section at T13, cats gradually recover hindlimb locomotion over a treadmill. Although initially well studied in kittens

(Grillner 1973; Forssberg *et al.* 1980*a,b*), this recovery is also prominent in the adult cat (Barbeau & Rossignol 1987; Bélanger *et al.* 1996; de Leon *et al.* 1998*a,b*; Rossignol *et al.* 2000, 2002) suggesting a great deal of plasticity even as adult. Figure 1*b* illustrates how, after a complete spinal section in the adult cat, intrinsic spinal mechanisms (CPG) coupled to increased sensory feedback may cooperate in the re-expression of locomotion.

Two to three days after spinalization, the cat is placed with its forelimb standing on an immobile platform above the treadmill while the hindlimbs are held over the moving treadmill belt. At this very early stage, the experimenter has to hold the hindquarters of the animal. Pinching the perineum or the base of the tail (sometimes the abdomen), some small alternate steps of the hindlimbs can be observed especially in more proximal joints (hip and knee movements) but the animal is incapable of plantar foot placement and walks on the dorsum of the foot. After 2–3 weeks of daily training on the treadmill, cats can walk with hindquarter weight support while making plantar foot contacts and generating much larger steps where the foot is placed in front of a line projecting from the hip joint to the ground. Perineal stimulation is no longer needed, but the animal must be prevented from falling on the side by holding the tail since all vestibulospinal and reticulospinal control of equilibrium has been lost.

In figure 2, kinematic measurements (angular displacement and stick figures) and EMG discharge of several muscles recorded in the same chronically implanted cat before (figure 2*a*), early (figure 2*b* at 8 days) and late (figure 2*c* at 21 days) after spinalization are illustrated. Even when the spontaneous locomotor pattern has recovered, step cycles remain generally shorter than prior to spinalization (compare stick figures in figure 1*a,c*). In most cases, there is some degree of foot drag at the onset of the swing phase, which can occupy up to one-third of the swing phase.

There are striking similarities between the EMG discharges of the same cat before and after spinalization although raw EMG recordings are frequently more 'choppy' since there is often an underlying clonus. The characteristic muscular discharge envelope, such as the gradual onset of the knee extensor (VL) and the abrupt onset of the ankle extensor (GL), is preserved. Discharge amplitude in extensor muscles may be overall reduced which probably corresponds to decreased weight support. Diminished weight support probably results from the loss of reticulospinal and vestibulospinal pathways. Indeed, similar deficits are observed with partial spinal lesions of ventral and ventrolateral spinal pathways as will be discussed later (Brustein & Rossignol 1998).

Timing characteristics between flexor muscles at different joints are often (but not always) altered in the spinal cat. For instance, in the intact cat, there is a delay between the initial burst of the knee flexor semitendinosus (St) and the burst of the hip flexor sartorius (Srt; see figure 2*a*, right). After spinalization (see figure 2*c*, right), the St and Srt muscles often start discharging at the same time, which may explain the observed foot drag. Indeed, knee flexors usually withdraw the foot before the hip flexors bring the limb forward. Since hip, knee and ankle flexions are

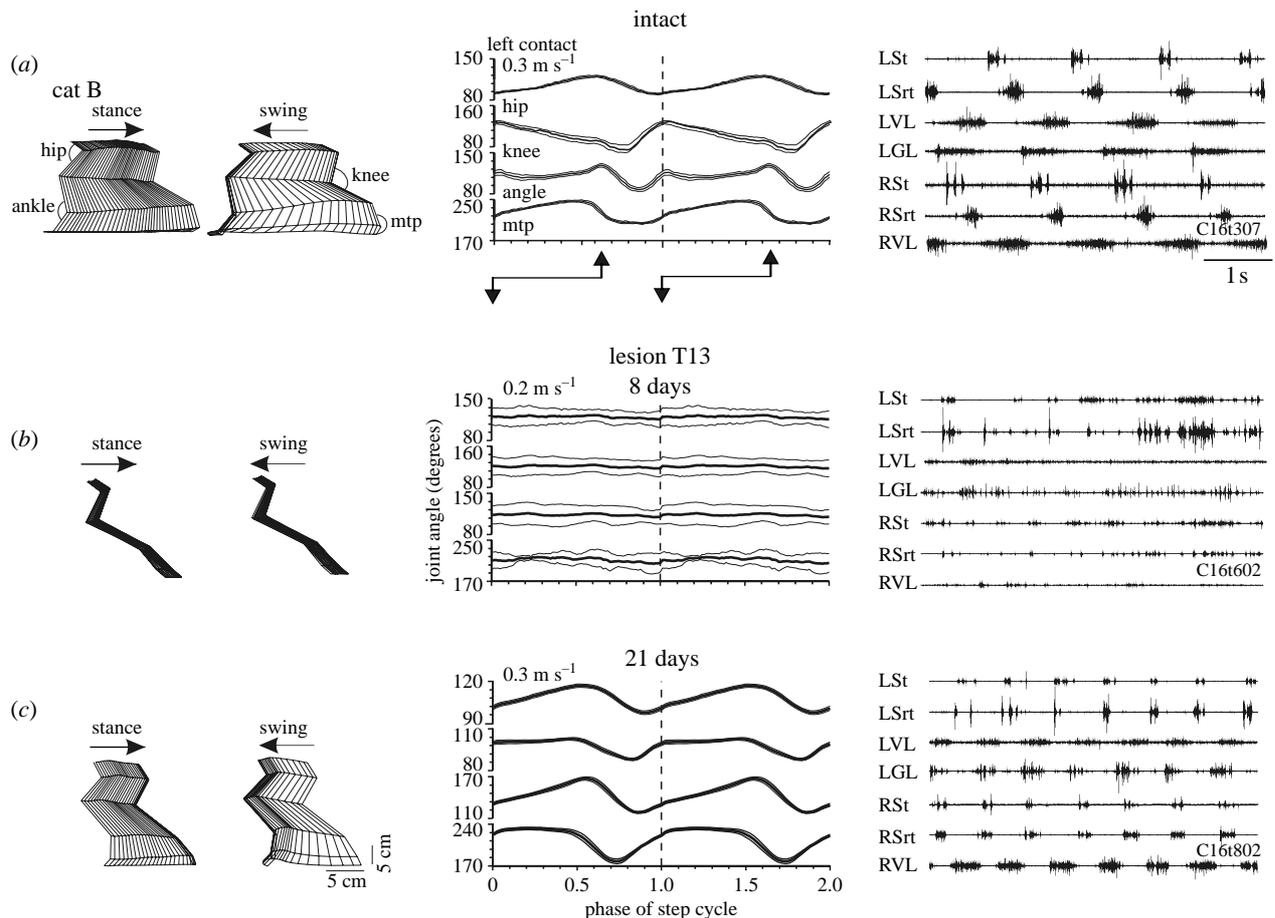


Figure 2. Comparison of treadmill locomotion of a cat in the intact condition and at two different days after a T13 spinal section. (a) Locomotor pattern in the intact state. (b) Locomotor pattern 8 days after spinalization. (c) Recovery of locomotion after 21 days of treadmill training. *Left column:* stick figures reconstructed from a video sequence of one-step cycle generated from a frame-by-frame video analysis displaying the swing and the stance phase separately. The orientations of joint measurements are given. Note that the calibration of the  $x$ -axis is twice that of the  $y$ -axis (see calibration in (c), left part of the figure). *Middle column:* angular excursion of the four joints (hip, knee, ankle and metatarsophalangeal (mtp)) averaged over 10 cycles. Paw contact (down arrow); paw lift (up arrow); stance phase (horizontal line). Flexion always corresponds to downward deflections of the angular traces. The treadmill speed is indicated in metres per second ( $\text{m s}^{-1}$ ) and is  $0.3 \text{ m s}^{-1}$  except for (b), which is at  $0.2 \text{ m s}^{-1}$  but the cat was not walking. *Right column:* raw EMG activity of the flexor and extensor muscles of the left (L) and right (R) hindlimb during locomotion. LSt, left semitendinosus; LSrt, left sartorius; LVL, left vastus lateralis; LGL, left gastrocnemius lateralis; RSt, right semitendinosus; RSrt, right sartorius; RVL, right vastus lateralis; and RGL, right gastrocnemius lateralis. The scale bar equals 1 s and applies to all EMG traces. Modified with permission from Langlet *et al.* (2005).

initiated more or less at the same time, the foot moves forward on the treadmill belt before it is lifted. Such specific deficits in the timing of hindlimb flexors may result from damage to corticospinal pathways since they are also seen after lesions of the dorsolateral tracts in the cat (Jiang & Drew 1996).

*Incomplete spinal sections.* In the context of locomotor plasticity, it is of great interest to perform restricted lesions of the spinal cord to study early deficits, which are related mainly to the destruction of some pathways and then to assess the time course and extent of locomotor compensation that results from the action of remnant pathways. The results of lesions of major tracts on the recovery of locomotion will be briefly reviewed and the reader is referred to previous reviews for more complete details (Grillner 1981; Armstrong 1986, 1988; Rossignol 1996; Grillner *et al.* 1997; Jordan 1998; Drew *et al.* 2004). It will be seen that none of the spinal quadrants, and, therefore, none of the descending pathways plays an indispensable role in the

basic generation of locomotion in the cat, although severe deficits may be observed as a result of deficient supraspinal controls.

*Ventrolateral pathways.* It is generally believed that locomotion is initiated via the activation of the mesencephalic locomotor region (MLR; Shik *et al.* 1966; Orlovsky & Shik 1976), which activates reticulospinal cells projecting down to the spinal cord and thus the central pattern generator (CPG) (see figure 1a). Various diencephalic and telencephalic structures project directly to the MLR and reticular formation (Grillner *et al.* 1997; Jordan 1998). Besides initiating locomotion, the reticular formation also plays a major role in the control of locomotion and associated posture (Shimamura *et al.* 1982; Drew *et al.* 1986; Mori 1987; Drew & Rossignol 1990a,b; Drew 1991; Perreault *et al.* 1993, 1994; Kably & Drew 1998a,b; Matsuyama & Drew 2000a,b; Prentice & Drew 2001; Drew *et al.* 2004; Matsuyama *et al.* 2004a,b). Thus, it should be expected that a lesion affecting reticulospinal pathways should

greatly impact locomotion. Although it is difficult to completely section the reticulospinal pathways, the consequences of major damage can be observed using ventral and ventrolateral lesions of the cord.

Based on the literature cited earlier, it was initially suggested that medial and mediolateral pathways were essential for locomotion (Eidelberg 1981). For locomotion to recover, a small part of a ventrolateral quadrant had to be spared (Afelt 1974; Eidelberg *et al.* 1981*a,b*; Contamin 1983). However, other experiments suggested that cats (Gorska *et al.* 1990, 1993*a,b*; Zmyslowski *et al.* 1993; Bem *et al.* 1995; Brustein & Rossignol 1999; Rossignol *et al.* 1999) and monkeys (Vilensky *et al.* 1992) could walk with the hindlimbs even after large lesions of these pathways at the last thoracic segment (T13). Similarly, humans who had a surgical section of ventral pathways for intractable pain retained walking ability (Nathan 1994).

In cats chronically implanted with EMG electrodes, ventral/ventrolateral pathways were sectioned bilaterally (Brustein & Rossignol 1998, 1999). With small lesions, cats could walk voluntarily at speeds of up to  $0.7 \text{ m s}^{-1}$  with all four limbs, 1–3 days after the lesion. However, with large lesions, which spared only part of the dorsal columns and various amounts of the dorsolateral quadrant, cats initially behaved as complete spinal cats. In open field, the forelimbs propelled the body but they dragged their hindquarters around over ground for a period of 3–6 weeks. With regular treadmill training, all cats regained voluntary locomotion of all the four limbs, although with the largest lesions, animals could not walk faster than  $0.4 \text{ m s}^{-1}$ . Hindlimb coupling remained stable at around 50% of the cycle. These cats walked with a more crouched position denoting a reduction in weight support ability. The hindlimb–forelimb coordination was at times unstable and cats often adopted a pacing gait, i.e. the fore- and hindlimbs on one side were in swing or in stance at the same time and alternated with the contralateral limbs. The fore- and hindlimb could even walk at slightly different mean frequencies leading to occasional stumbling. Precise measurements of the forelimb–hindlimb coupling showed a gradual drift over several cycles that led to stumbling. When walking up-slope there was an increase in the amplitude of the forelimb elbow extensors to compensate for increased load. The amplitude of extensor burst in the hindlimbs did not compensate during up-slope walking due to the lack of supraspinal compensatory signals. On force platforms, the forelimbs became propulsive in contrast to the normal situation where the hindlimbs are propulsive. Despite some walking instability on the treadmill, it is remarkable that at this stage cats could voluntarily stand up, walk around and overcome natural obstacles on the ground or treadmill.

Horseradish peroxidase (HRP) was injected below the spinal lesion at the conclusion of the experiment to evaluate the number and location of spinally projecting cells. In the pontine reticular and medullary reticular formations, labelled cells accounted for 5–48% of normal values depending on the size of the spinal lesion. Vestibulospinal neurons were virtually wiped out. Counts of rubrospinal cells were either normal or somewhat decreased since some lesions may have

encroached rubrospinal axons. The remaining reticulospinal and rubrospinal cells may have participated in the recovery of locomotion. Although propriospinal neurons were not studied, they could be strategically placed to participate in such compensation as suggested by others (Jordan & Schmidt 2002; Bareyre *et al.* 2004). However, preliminary evidence suggests that the number of HRP-labelled cells was higher in the motor cortex of lesioned cats compared with control cats and their distribution was somewhat more lateral (Rossignol *et al.* 1999), suggesting that a significant compensation from corticospinal pathways may contribute to locomotor recovery.

Dorsolateral pathways. Cats can walk over ground after large lesions of the dorsolateral white matter (Gorska *et al.* 1993*b*; Zmyslowski *et al.* 1993; Bem *et al.* 1995). In more quantitative studies of treadmill locomotion after lesions of the dorsolateral funiculus, which included the dorsal columns (Jiang & Drew 1996), it was shown that voluntary quadrupedal locomotion is impaired for 3–10 days. Cats adopted a more crouched posture during walking for a period of 2–3 weeks and step-cycle duration was increased due to a prolongation of stance, which is contrary to cats with ventrolateral lesions where step cycles of individual hindlimbs close to normal were observed. On the contrary, cats with dorsolateral lesions had changes in intra-cycle characteristics. For instance, there was simultaneous onset of the knee flexor St with the hip flexor Srt. As mentioned earlier, there normally exists a delay between the two with St discharging before Srt, which potentially underscores persistent foot drag. Contrary to ventrolateral lesions, cats with dorsolateral lesions are unable to voluntarily modify their gait to step over an obstacle on a treadmill (Drew *et al.* 1996). Finally, in cats with dorsolateral lesions, both fore- and hindlimbs participate in compensating for treadmill slopes.

Hemisectons. Hemisectons of the cord have been studied in various animal preparations, but there are a number of inconsistent reports on the deficits and recovery of locomotion. Nevertheless, there is an agreement that the hindlimb ipsilateral to the lesion gradually recovers locomotion within approximately one month (Eidelberg *et al.* 1986; Basso *et al.* 1994; Kuitz-Buschbeck *et al.* 1996). Remaining deficits following this period are not consistent among authors. In one study using precise kinematic measures (Kuitz-Buschbeck *et al.* 1996), the permanent deficit is a shortening of stance and a prolongation of swing on the side of the lesion leading to some asymmetrical gait. A reduction in stance is compatible with an inability to support weight (as seen in the complete spinal cat). The slowing of the swing phase might in turn be related to the lesion of the corticospinal tract (CST), although the timing abnormalities seem to differ compared with dorsolateral tract lesions (Jiang & Drew 1996). There is also a variable degree of spasticity manifested as a reduced yield during the E2 phase of locomotion (Kuitz-Buschbeck *et al.* 1996). Although the role of descending intact tracts were considered important for the recovery of locomotion after hemisection, sprouting of afferents was proposed as a major player in this recovery (Basso *et al.* 1994). However, other work

suggests that afferent fibre sprouting caudal to the lesion does not greatly differ between the lesioned and intact sides (Nacimienta *et al.* 1993).

#### Pharmacology

Previous sections indicated a functional locomotor recovery resulting from a reorganization of pathways at several levels. However, the plasticity in connections can also stem from changes in responsiveness to pharmacological agents and/or changes in the density of various neurotransmitter receptors.

**Neurotransmitter agonists.** Early work using the noradrenaline precursor 3,4-dihydroxy-L-phenylalanine (L-DOPA) in acute spinal cats (Jankowska *et al.* 1967*a,b*) led to the concept of a central pattern generator for locomotion (Grillner & Zangger 1979). Indeed, after an i.v. injection of L-DOPA, the characteristic discharge pattern recorded in flexor and extensor nerves (electroneurograms) during fictive locomotion shared many similarities with EMG patterns recorded in the walking cat. Therefore, specific chemicals can trigger the activity in an extant autonomous spinal circuitry since cats were both spinalized and curarized. As mentioned earlier (see figure 1*a*), this central pattern generator concept is central to our understanding of locomotor control. This seminal work was followed by other studies attempting to determine which receptors of which neurotransmitter systems activate the CPG with the aim of applying such pharmacological tools in the rehabilitation of locomotion after spinal injury in animals and particularly humans.

First, agonists of different subtypes of adrenergic receptors were used. The  $\alpha$ -2 noradrenergic agonist, clonidine, was first used in acute spinal cats (Forssberg & Grillner 1973) and it was found that a well-developed bilateral hindlimb walking pattern could be evoked within minutes of the clonidine injection in about one-third of cats. It is important to realize that with appropriate neurochemical stimulation, even after acute spinalization, cats can walk with the hindlimbs. Therefore, recovery of spontaneous locomotion in chronic spinal cats must then represent plastic changes in the pathways leading to the activation of this extant spinal pattern generator more than in the CPG itself.

Following this work, we have found that, in adult spinal cats chronically implanted with EMG electrodes, only the  $\alpha$ -2 adrenergic agonists, such as clonidine, injected intraperitoneally (Barbeau *et al.* 1987*a*), or similar agonists (tizanidine, oxymethazoline) injected intrathecally (Chau *et al.* 1998*b*) induce locomotion shortly after spinalization. Later on, when cats have regained spontaneous locomotion, these noradrenergic agonists still exert potent effects on the locomotor pattern by increasing EMG burst duration and overall step length. There are, however, smaller changes in the burst amplitude. In the present context of plasticity of connection, it is worth mentioning that the effects of clonidine differ, whether the cats have an intact spinal cord, a complete or a partial spinal lesion (Rossignol *et al.* 1998, 2001). Whereas in the intact state intrathecal injection of clonidine has little effect, it has, in the same cat but early after spinal section the striking effect of evoking locomotion (Giroux *et al.*

2001). Furthermore, in cats with a large ventral and ventrolateral lesion, an intrathecal clonidine injection can altogether stop voluntary quadrupedal locomotion (Brustein & Rossignol 1999). Therefore, the state of receptivity of receptors as well as the presence of pre- and postsynaptic receptors in various neural elements may differ in different models of spinal lesion, and this will determine the effects of the drugs. This is important when assessing drugs in humans since the extent of the lesion is not known most of the time (Remy-Neris *et al.* 1999).

Serotonergic agonists such as quipazine, 5-methoxy-*N*, *N*-dimethyltryptamine or the precursor 5-hydroxytryptophan do not initiate locomotion in acute spinal cats (Barbeau & Rossignol 1990). As will be seen later, this is a major difference between cats and rodents. The reason for the inability of 5-HT agonists in evoking locomotion might be related to the level of the spinal section as suggested by others (Schmidt & Jordan 2000) on the basis of the segmental distribution of 5-HT receptor subunits important for locomotion. Therefore, the level of section may be important in evaluating the effects of stimulation by certain drugs since the receptors on which they are acting as well as their state of responsiveness may differ in different preparations (intact cord, complete or incomplete spinal section). Although 5-HT agonists do not initiate locomotion in spinal cats, they increase the output amplitude of activity of hindlimb muscles (especially extensors) and paraxial muscles (Barbeau & Rossignol 1990). In cats with ventrolateral spinal lesions, 5-HT agonists increased weight support as well as the endurance of the cats to walk uninterruptedly (Brustein & Rossignol 1999). Importantly, these pharmacological effects were well integrated in an otherwise voluntarily generated locomotor pattern, suggesting that voluntary commands could make best use of the increased spinal excitability provided by the pharmacological stimulation.

Shortly after spinal section in cats, intrathecal injections of *N*-methyl-D-aspartate (NMDA), contrary to *in vitro* neonatal rats or lampreys and in contrast with decerebrate cats (Douglas *et al.* 1993), does not induce locomotion but generates tremor and toe fanning (Chau *et al.* 2002; Giroux *et al.* 2003). However, when injected intrathecally in spinal cats that just started to generate small steps (around 6–7 days), NMDA could boost emergent locomotor patterns for several hours (Chau *et al.* 2002). NMDA had little effects *per se* on the spontaneously recovered locomotor pattern several weeks after spinalization.

**Neurotransmitter antagonists.** The use of various neurotransmitter antagonists is of interest not only to block the effects of previously described effects of agonists in the spinal cat but also in determining the role that certain receptors may play in the spontaneously generated locomotor pattern in the intact or spinal cat.

Yohimbine, an  $\alpha$ -2 adrenergic blocker, reverses the effect of clonidine on the initiation of locomotion or the clonidine-induced change in the step cycle (Barbeau *et al.* 1987*a*; Giroux *et al.* 2001). However, yohimbine has no effect in the chronic spinal cat walking on a treadmill. Although this might appear obvious since the neurotransmitter is no longer present following

spinalization, it is important to block these receptors to show that residual noradrenaline and other molecules that could potentially activate these receptors are not responsible for the ability of the cat to walk. However, yohimbine induces, in the intact cat, an important incoordination of the fore- and hindlimbs and an inability to adequately control the trunk and hindquarters that can often walk sideways relative to the forelimbs (Giroux *et al.* 2001) suggesting that in normal locomotion, noradrenergic neurotransmission is important for interlimb coordination (McDermid *et al.* 1997).

Since 5-HT does not induce locomotion in the cat, less evidence is available on 5-HT blockers. However, one study showed that cyproheptadine greatly reduces the enhanced muscular output induced by 5-HT agonists in spinal cats (Barbeau & Rossignol 1990, 1991). No data were obtained yet on intact cats.

Aminophosphonopentanoic acid (AP-5), an NMDA blocker, was shown to influence locomotion in the intact cat by reducing its weight support. However, the cat had no difficulty in compensating for this deficit and could continue walking on the treadmill. In the very same cats, which had received AP-5 in the intact state without effect, the same drug completely blocked the spontaneously generated locomotion after spinal transection (Giroux *et al.* 2003). This suggests that NMDA receptors play a crucial role in generating spinal locomotion and that minor effects observed in the intact cat after AP-5 injection probably result from compensation by other neurotransmitters released by intact descending pathways, which are absent in the spinal cat.

Thus, in the weeks after spinalization, one of the major changes that occur is a basic transformation of the central spinal circuitry which normally operates through a balance of various neuromodulators (including monoamines) to a more restricted set of transmitters/modulators acting on glutamatergic receptors. Furthermore, the key role played by afferent inputs in spinal locomotion (see later) may be related to their ability to release neurotransmitters capable of activating the locomotor spinal circuitry.

*Evolution of receptors after spinalization.* In an attempt to study the plastic changes in the cord after spinalization, the distribution of  $\alpha_1$ -,  $\alpha_2$ -noradrenergic and serotonin<sub>1A</sub> (5-HT<sub>1A</sub>) receptors was studied in the spinal cords of normal cats as well as in cats spinalized at T13 a few weeks or months earlier (Giroux *et al.* 1999). Binding densities of  $\alpha$ -1 and  $\alpha$ -2 receptors significantly increased in the lumbar segments at 15–30 days after spinalization. At longer survival times (three or more months), binding densities returned to near control values. The 5-HT<sub>1A</sub> receptors also followed the same profile of upregulation and returned to control values. The marked upregulation of various monoaminergic receptors observed after spinal section is therefore a clear example of the plasticity of connections occurring in the adult. However, although the timing appears appropriate, the links between these receptor changes and recovery of locomotor capabilities have not yet been established. This might explain why larger doses of clonidine are usually needed to induce locomotion in the acute stage of spinalization. When receptors are upregulated, smaller doses of clonidine are efficacious.

However, even after several months, clonidine is still very effective at very low doses suggesting that other intracellular mechanisms that may increase receptor coupling with intracellular events become important with time (Reader *et al.* 2001).

Preliminary work on  $\alpha$ -amino-5-hydroxy-3-methyl-4-isoxazole propionic acid (AMPA) receptors shows an upregulation but, contrary to aminergic receptors, it appears that this upregulation is maintained (Chau *et al.* 2001), consistent with the fact that glutamatergic receptors are important, for long-term maintenance of spinal locomotion.

Preliminary work has been done to determine the segmental and laminar distribution of various types of receptors (Rossignol *et al.* 2002). There are indications that the upregulation differs according to segments (being highest in the midlumbar segments; Rossignol *et al.* 2002) but this must be confirmed because it has implications for determining the importance of the level of spinal transection for locomotor recovery.

#### *Level of spinal section*

The level of spinalization in the recovery of locomotion is important on several counts. A better understanding of spinal levels implicated in the generation of locomotion might be extremely useful in optimizing strategies when using spinal electrical stimulation, pharmacological stimulation through intrathecal delivery systems or through grafts of cells releasing biogenic amines. In the context of plasticity of connections, it might also suggest how intersegmental reconnections are important for the re-expression of locomotion.

Our initial work using intrathecal delivery of drugs indicated that application of drugs at rostral segments of the spinal cord in cats (at around L4) were very effective in triggering or modulating locomotion (Chau *et al.* 1998a,b; Giroux *et al.* 2001). Further work showed that, in cats spinalized one week earlier, an intraspinal injection of clonidine or yohimbine, restricted to the L4 segment, initiated or blocked the spinal locomotion, respectively (Marcoux & Rossignol 2000). It should be recalled that this spinal level in the cat is rostral to the main hindlimb motor neuron pools (Vanderhorst & Holstege 1997). In such experiments, it was also shown that a lesion at caudal L4 abolished all spinal locomotion even after i.v. injections of clonidine. It was unclear whether this constituted a second spinal shock or a disconnection of specific spinal segments critical for locomotion. Indeed, previous work by others suggested that neural elements in these segments are critical for locomotion (Shefchyk *et al.* 1990; Jankowska & Edgley 1993; Davies & Edgley 1994; Jankowska *et al.* 2003).

A series of experiments was performed on cats spinalized at T13 and trained to recover locomotion of the hindlimbs on the treadmill. Thereafter, each cat was submitted to a second complete spinal section and their locomotor ability was re-assessed over several weeks or months (Langlet *et al.* 2005). A second spinalization at L2 or rostral L3 did not significantly alter the ability of the cats to walk (see figure 3), eliminating the hypothesis that a second spinal shock is responsible for the effects seen after a second lesion at

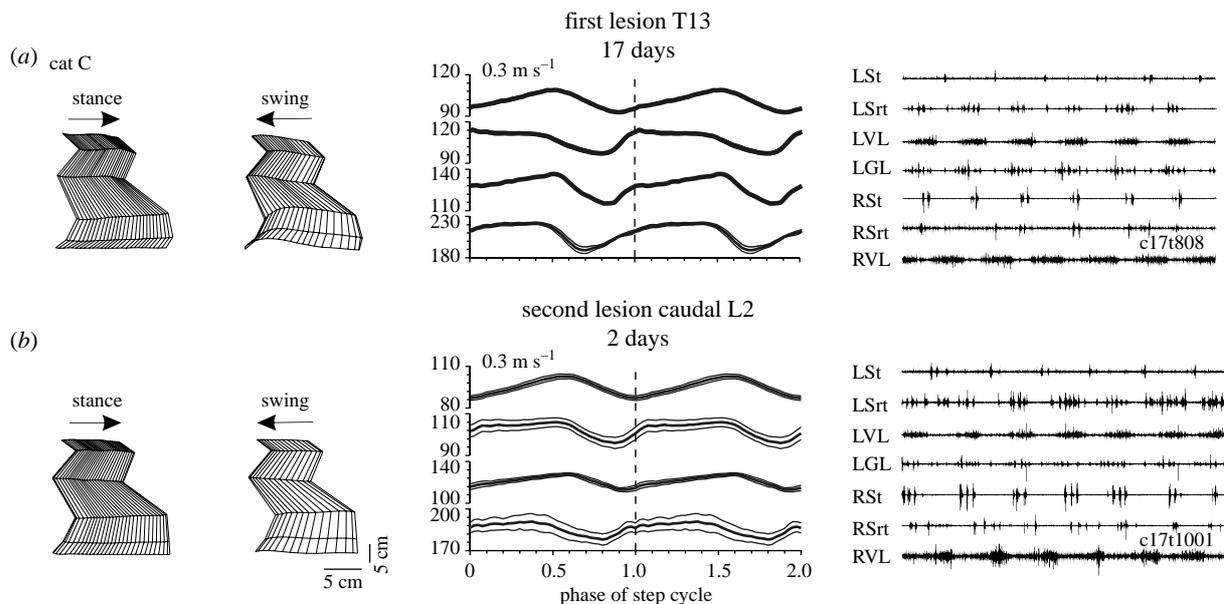


Figure 3. Comparison of recovery of locomotion after a second spinal lesion at the caudal part of L2 segment. Stick diagrams, angular displacement and raw EMG traces of hindlimb flexor and extensor muscles are as displayed in figure 3. (a) Recovery of locomotion after a first transection at T13 after 17 days of training. (b) Locomotor performance 2 days after the second lesion at the caudal L2 level in the same cat. Modified with permission from Langlet *et al.* (2005).

L4 reported earlier. However, when the second chronic lesion was at caudal L3 or L4 (see figure 4), locomotion was completely abolished and could not be reinstated even after 3–4 weeks of locomotor training. Although locomotion was not expressed, it was remarkable to find that other rhythmic activities, such as fast paw shake, were not only present but also enhanced (figure 4, bottom right). Therefore, the spinal cord below the lesion has the capacity to generate rhythmic activity but not locomotion. This also indicated that motor neurons of recorded muscles were undamaged by the lesion and other neural elements important for triggering locomotion are located at or above L4. We do not yet know which interneuronal system plays such a crucial role, but it is probable that interneurons identified in these regions are important (Edgley *et al.* 1988; Shefchyk *et al.* 1990). It is also conceivable that propriospinal interneurons in the rostral cord (Shik 1997; Jordan & Schmidt 2002), after section, become 'leaders' to coordinate spinal locomotion, which may underlie plastic changes in connectivity. Such interneuronal plasticity remains to be characterized, but other work (Jordan & Schmidt 2002) has shown using *c-fos* labelling, after intensive locomotion in decerebrate cats, that cholinergic propriospinal interneurons are numerous, which suggests the possibility of plastic changes in interneuronal populations.

Finally, midlumbar segments may be important in evoking locomotion by other means. It was recently shown that intraspinal electrical microstimulation applied at different spinal levels could initiate locomotion in one-week spinal cats (Barthélemy *et al.* 2005). After inactivating these midlumbar segments by yohimbine or performing a second lesion at caudal L4, locomotion could no longer be evoked by intraspinal microstimulation (Barthélemy *et al.* 2002; Rossignol *et al.* 2002). Whether or not these segments are essential for evoking locomotion via brainstem

stimulation is still under study (Leblond & Rossignol 2003).

#### Role of sensory inputs in locomotion

The role of sensory afferents in locomotion is important and increasingly so for locomotor recovery after spinal lesion. The recovery of spinal locomotion probably depends on proper stimulation of afferent inputs by locomotor training. Training leads to specific motor improvements (Edgerton *et al.* 1997) and accelerates the recovery of spinal locomotion when provided early after a spinal lesion under proper pharmacological stimulation (Chau *et al.* 1998a; Rossignol *et al.* 2001).

Within the context of this review, it is only possible to give a general overview of the role of afferents during locomotion and how transmission in reflex pathways may be changed after a spinal lesion, thus giving an indication that even the simplest reflexes undergo plastic changes after spinal lesion even in the adult. For a broader review on the topic of sensorimotor interactions during locomotion, the reader is referred to a recent review (Rossignol *et al.* 2006). At the onset, however, it should be stated that dorsal rhizotomy in the acute decerebrate cat (Grillner & Zangger 1984) or chronic dorsal rhizotomy (Wetzel *et al.* 1976; Goldberger 1977) does not prevent locomotion, although obviously it precludes adaptation of the pattern to the external environment. Similarly, after neurochemical paralysis, which abolishes all phasic sensory inputs, neurochemical activation by DOPA (Grillner & Zangger 1979) or other noradrenergic agents (Pearson & Rossignol 1991) or by brainstem stimulation (Jordan *et al.* 1979) can induce locomotion. Finally, pyridoxine intoxication, which removes large diameter sensory afferents, does not prevent the long-term recovery of locomotion despite an initial inability to walk (Pearson *et al.* 2003). In real life, of course, sensory inputs have important adaptive roles.

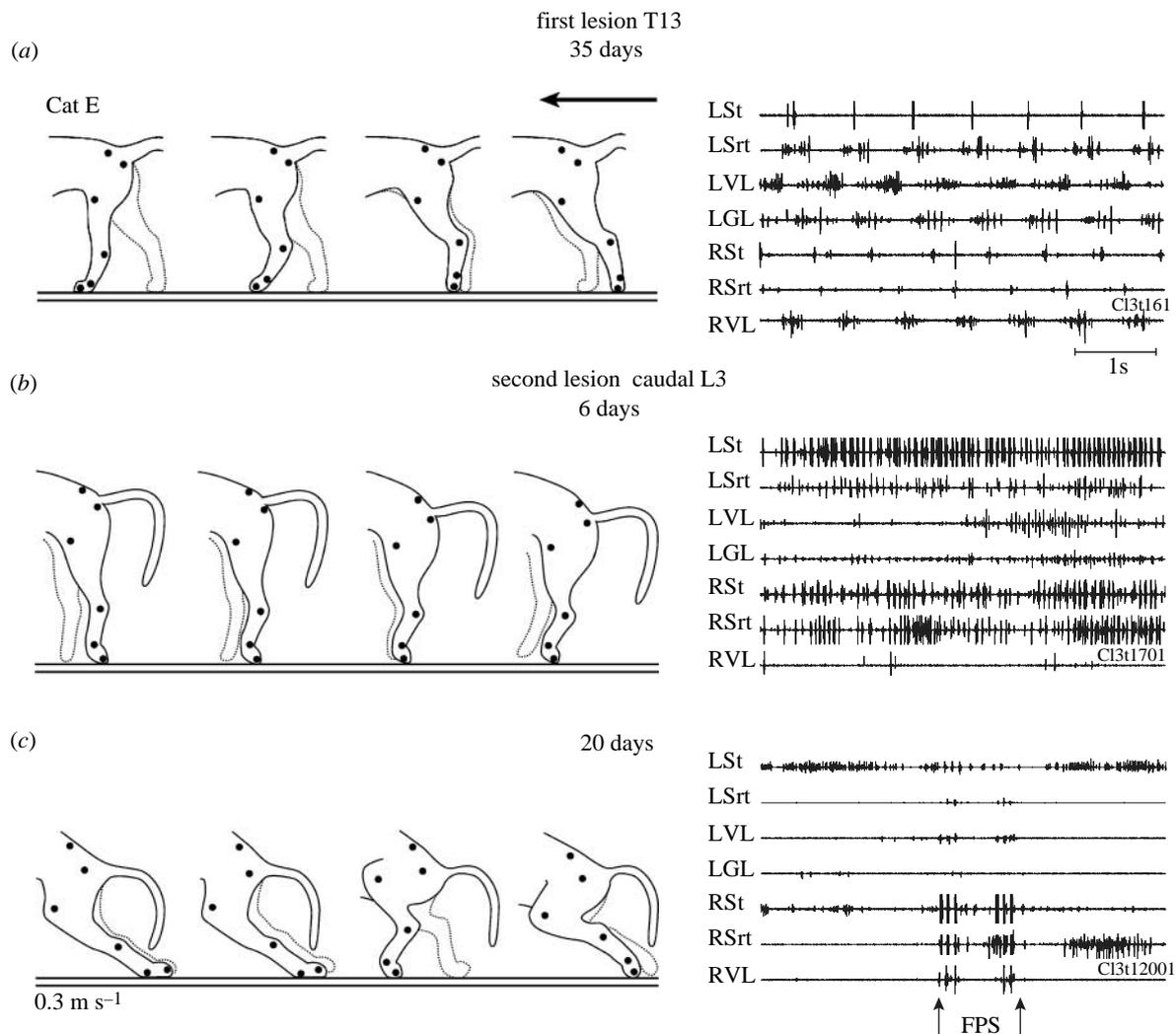


Figure 4. Abolition of locomotion after a second spinal transection at caudal L3. Figurines drawn from the video recordings show the hindlimb position. (a) Spinal locomotion after 35 days of training following a first transection at T13. (b) Absence of locomotion 6 days after a second lesion at caudal L3. Only tonic activity of the flexors (St and Srt) was observed. (c) Absence of locomotion following 20 days of training after the caudal L3 lesion. Some small movements of flexion and extension were observed but no locomotion. Note the presence of spontaneous fast paw shakes (FPS), a rhythmic pattern which has a much faster frequency than locomotion. Modified with permission from [Langlet \*et al.\* \(2005\)](#).

Proprioceptive afferents (groups Ia, Ib and II) appear to regulate in part the duration of various sub-phases of the step cycle (step frequency and speed) as well as the discharge amplitude of muscles. For instance, protracting the hip joint or the shoulder joint generally lengthens the step cycle and stops walking if it reaches the maximum limit ([Pearson & Rossignol 1991](#); [Saltiel & Rossignol 2004a](#)). A retraction has the opposite effect and speeds up the cycle. Phasic protraction of the shoulder during fictive or real locomotion ([Rossignol \*et al.\* 1993](#); [Saltiel & Rossignol 2004b](#)) or imposed protraction of the hindlimb during swing ([Lam & Pearson 2001](#); [McVea \*et al.\* 2005](#)) shortens the swing phase during real locomotion whereas protraction during the stance phase of fictive locomotion prolongs swing. This indicates very well that although fictive locomotor rhythms can be evoked in spinalized and curarized animals, when present, proprioceptive afferent feedback participates in the regulation of the step cycle.

Similarly, the amplitude of muscle discharge can be regulated by proprioceptive afferent feedback. It has

been proposed that 40–60% ([Donelan & Pearson 2004a](#)) of the amplitude of ankle extensor discharge depends on afferent feedback. Thus, during unloading a human subject walking on a treadmill, there is a major reduction in EMG amplitude ([Harkema \*et al.\* 1997](#); [Dietz & Colombo 1998](#); [Dietz & Duysens 2000](#)). If the ankle extensors are unloaded during stance by mechanically extending the ankle through an external ankle brace, a 50% decrease in EMG amplitude of the ankle extensor muscle ensues ([Sinkjaer \*et al.\* 2000](#)). In cats, elegant experiments have been performed to evaluate unloading during locomotion, in particular ‘foot-in-the hole’ experiments in which cats suddenly make one step through a trap ([Gorassini \*et al.\* 1994](#)) or walk on a peg, which is lower than expected ([Donelan & Pearson 2004b](#)). In all these cases, where sensory feedback is reduced presumably because of a decrease in ankle extensor load, there is a short latency reduction in ankle extensor muscle activity.

Cutaneous inputs, on the other hand, appear to have a major role in positioning the foot during locomotion. In humans ([Zehr \*et al.\* 1998a,b](#); [Zehr & Stein 1999](#)),

cats (Rossignol *et al.* 1988, 2006; Rossignol 1996; Bouyer & Rossignol 2003a) and rats (Schouenborg 2003), an exquisite number of reflexes are used to correctly place the foot after electrical or mechanical stimulation. Given the multisynaptic nature of cutaneous pathways, it can be expected that these are highly plastic and considerably modified after spinal lesions.

*Changes in reflex pathways after chronic spinalization.* After chronic spinal hemisection (Hultborn & Malmsten 1983a,b) or complete spinal section (Hochman & McCrea 1994a), the spasticity observed has been attributed to changes in reflex pathways although precise underlying mechanisms are unclear and appear to differ in various motor neuron pools and even in various types of motor neurons (Hochman & McCrea 1994c). In the anaesthetized cat, six weeks after complete cord section, homonymous monosynaptic Ia EPSPs in lateral gastrocnemius (LG) can almost double, whereas in other ankle extensors, changes in amplitude are non-existent or minimal. Heteronymous excitatory post-synaptic potentials (EPSPs) are also markedly increased not only in LG but also in medial gastrocnemius (MG), suggesting that these changes are not due to changes in membrane properties of motor neurons since homonymous EPSPs in MG motor neurons are unchanged. The rise time and half width of these EPSPs are also diminished and these changes cannot be wholly attributed to the minimal changes in membrane properties seen in motor neurons after spinalization (Hochman & McCrea 1994b) and must therefore be attributed to changes in other control mechanisms such as presynaptic inhibition or to changes in the efficacy of some synapses close to the soma. However, it was more recently shown in rats which develop tail spasticity after a low sacral spinal section that plateau potentials return in motor neurons and might in part be responsible for the spasticity and increase in some reflex responses (Bennett *et al.* 2004; Li *et al.* 2004; Heckmann *et al.* 2005).

Changes in other pathways have been documented after spinalization in animals and humans such as an increase in recurrent inhibition (Hultborn & Malmsten 1983b; Shefner *et al.* 1992) and a decrease in reciprocal inhibition (Xia & Rymer 2005). Flexion responses following spinalization are increased (Sherrington 1910).

*Changes in reflex pathways after locomotor training.* Interesting studies were performed in spinal cats that were either trained or not (shams) on a treadmill to determine if training influenced transmission in reflex pathways. Monosynaptic excitation, disynaptic inhibition and polysynaptic excitation were studied in a terminal experiment in trained and sham chronic spinal cats (Côté *et al.* 2003). The changes were first quantified at rest in the absence of fictive locomotion. It was found that locomotor training significantly decreased monosynaptic excitation and disynaptic inhibition evoked by 1b afferent stimulation. Disynaptic inhibition could even be reversed by clonidine to a polysynaptic excitation even without locomotion. During fictive locomotion, similar changes were observed. Figure 5 gives a summary of these changes in various pathways.

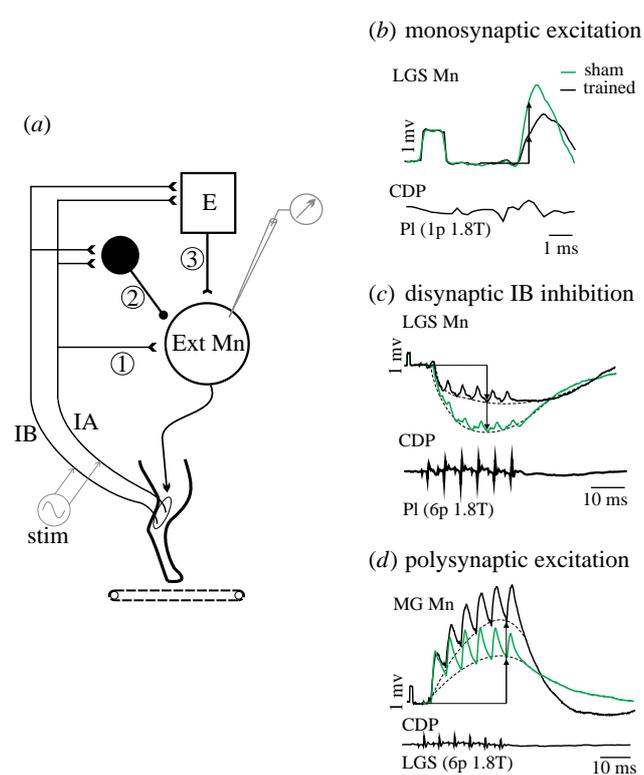


Figure 5. Evaluation of the effect of locomotor training on load pathways. (a) Spinal proprioceptive pathways under study. A schematic of three sensory pathways transmitting inputs from muscle group I afferents to ExtMn is shown to the left: the monosynaptic (stretch reflex) pathway (from group Ia afferents originating in muscle spindles of extensors), the disynaptic inhibitory pathway (from group Ib afferents of extensors originating in Golgi-tendon organs plus some group Ia fibres) and the polysynaptic excitatory pathway (from groups Ib and Ia afferents of extensors). In the acute spinal cat, this latter pathway shares interneurons with the network generating the excitatory locomotor drive in extensors (box E). Sample records of motor neuronal postsynaptic potentials used for measurements are on the right. (b) The amplitude of monosynaptic EPSPs was measured at a latency of 1.4 ms (rising phase in this example, i.e. just before the onset of possible disynaptic components). Note that compared to the sham (green), the monosynaptic reflex is decreased after locomotor training (black). (c) The disynaptic Ib inhibition was evoked by a short train of stimuli (six pulses, 1.4–2.0 T, 200–300 Hz), and the inhibitory post-synaptic potential (IPSP) amplitude was measured at the maximal negative deflection in the intracellular trace. Note that there were often monosynaptic EPSPs (six positive humps) overriding the inhibitory trough (dotted line). It is clear that locomotor training reduces the maximal disynaptic inhibition. Afferent volley was monitored by recording the cord dorsum potential (CDP). (d) Polysynaptic excitation was evoked by a similar short train of stimuli, and the amplitude was measured at the maximal positive deflection (dotted line) underlying monosynaptic EPSPs. Modified with permission from Côté *et al.* (2003).

It is believed that observed changes could reduce spasticity (reduction in 1a afferent transmission) and increase the recruitment of extensor motor neurons (ExtMn) for the recovery of weight-bearing locomotion. Again these changes are not due to alterations in membrane properties of the motor neurons since no correlation could be established between the changes

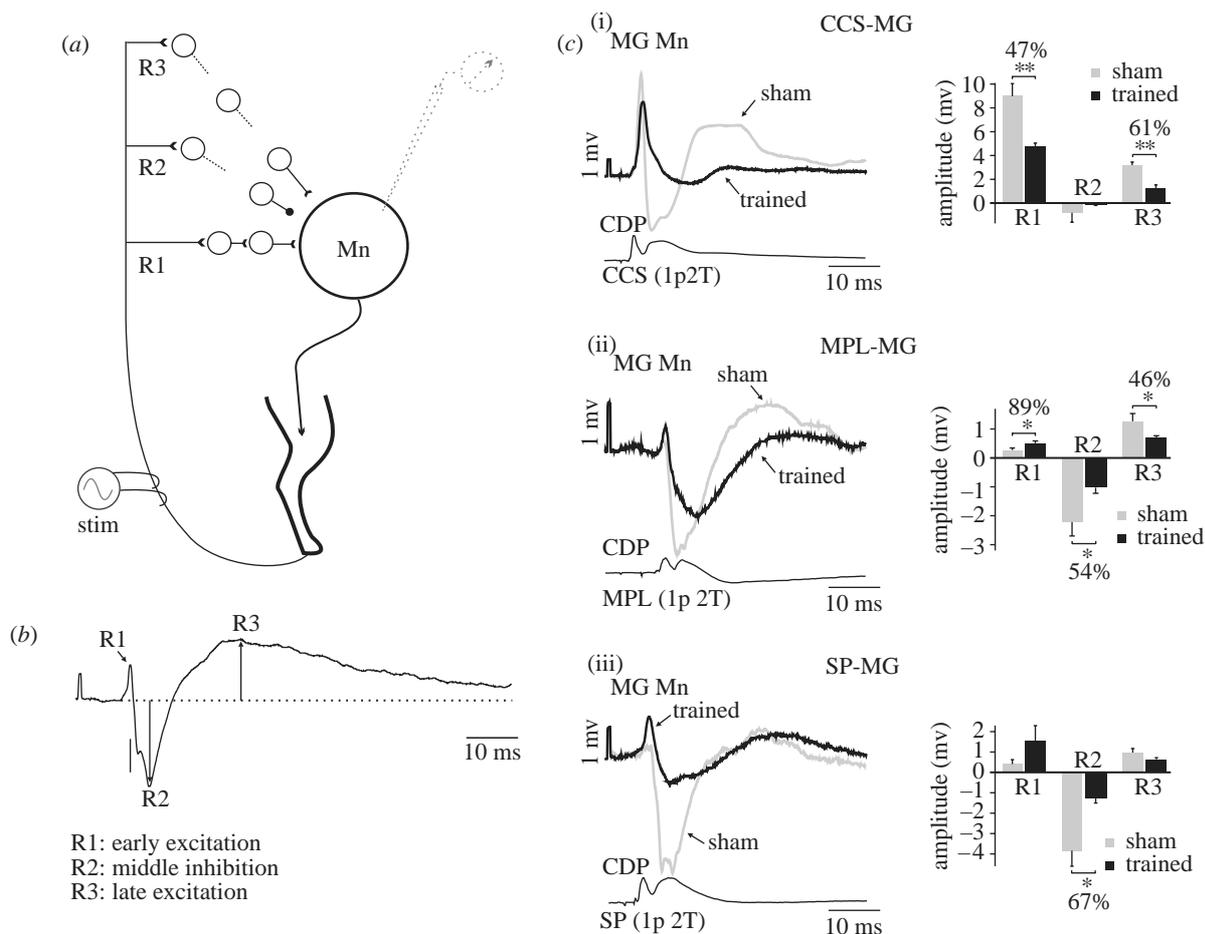


Figure 6. Evaluation of the effect of locomotor training on cutaneous pathways. (a) Hypothetical cutaneous pathways leading to responses of various latencies (R1, R2 and R3) are illustrated. (b) Type of responses to cutaneous stimulation recorded in motor neurons. Representative averaged post-synaptic potential patterns ( $n=62$ ) evoked by cutaneous afferents (caudal cutaneous sural (CCS), medial plantar (MPL) or superficial peroneal (SP)) recorded in extensor or flexor/bifunctional motor neurons are shown. The initial depolarization is referred to as R1 (early excitation), the subsequent hyperpolarization as R2 (middle inhibition) and the following depolarization as R3 (late excitation). (c) Training specifically modified transmission from cutaneous afferents to the MG motor pool. Left: PSPs ( $n \geq 40$ ) evoked by stimulation of (i) CCS, (ii) MPL and (iii) SP afferents recorded in MG motor neurons with similar AHPs (range 70–91 ms) in a sham (grey) and a trained cat (black). Right: histograms of the mean amplitude of responses evoked by (i) CCS, (ii) MPL and (iii) SP afferents recorded in all MG motor neurons in shams (grey) and trained cats (black). Six of the nine pathways tested in MG motor neurons were modified by training. Significant differences are indicated as follows:  $*p < 0.05$ ;  $**p < 0.01$ . Overall, training (i) decreased both CCS-MG-R1 (by 47%) and CCS-MG-R3 (by 61%) amplitudes, (ii) increased MPL-MG-R1 amplitude (by 89%), decreased MPL-MG-R2 (by 54%) and MPL-MG-R3 (by 46%) amplitudes and (iii) decreased SP-MG-R2 amplitude (by 67%). Mn, motor neuron. Modified with permission from Côté & Gossard (2004).

observed and the after-hyperpolarization (AHP) of motor neurons, which reflects the membrane time constant and input resistance. The changes are rather attributed to excitability changes of interneurons receiving group I inputs to explain the reduced autogenic inhibition and to increases in the output of presynaptic interneurons on group Ia afferent terminals, which can reduce monosynaptic excitation.

Interestingly, reflexes evoked by so-called flexor reflex afferents (FRAs) generated crossed activation of flexor motor neurons rather than ExtMn, suggesting an important reorganization of specific reflex pathways or at least a significant change in bias since both crossed extensor and crossed flexor pathways exist (Safyants 1970; Rossignol & Gauthier 1980; Gauthier & Rossignol 1981).

Furthermore, cutaneous pathways show reduced excitability specifically from foot pads (from the medial plantar nerve) after locomotor training (Côté &

Gossard 2003), again suggesting that training diminishes hyperreflexia from the foot pads after spinalization. Figure 6 schematically illustrates the pathways involved, the various responses observed and the changes after locomotor training.

The relationship between the changes in proprioceptive and cutaneous pathways induced by locomotor training and the actual improvement of locomotor performance is an important question and may justify major efforts in attempting to normalize the gain of reflex pathways after SCI in order to achieve the best possible locomotor performance.

*Plastic changes after neurectomies.* The functional recovery of locomotion after spinal lesions suggests changes occurring within the spinal cord to optimize the remaining circuitry controlling locomotion. The above reflex changes occurring during locomotor training suggest a great deal of plasticity in the spinal

cord after lesion and the possibility of influencing this plasticity. In the last decade or so, we have performed various experiments to demonstrate spinal plasticity, i.e. a functional compensation achieved solely by the spinal cord in absence of descending inputs. Whereas studies on locomotion demonstrate some type of plasticity, the fact that there exists a spinal pattern generator (Grillner & Zangger 1979) and spinal kittens can express locomotion even if the spinalization has occurred before having had the chance to walk clearly suggests a largely hardwired spinal pattern generator (Forssberg & Svartengren 1983). Thus, the expression of locomotion after spinalization is not the result of learning a new pattern but the result of re-expressing a spinal component of the overall locomotor program. That specific training can promote aspects of this motor control (bias on alternation or bias on postural control; Hodgson *et al.* 1994) reveals that the pattern generator, although hardwired, can still be modulated by biasing some of its components and this training can have long-term effects (de Leon *et al.* 1999).

To demonstrate spinal plasticity more directly, we studied how cats adapt their locomotor pattern after a nerve section either in the intact state or after spinalization and we have compared the compensation occurring in both states in the same cat. To this end we have severed muscle nerves and cutaneous nerves of the hindlimbs.

Muscle nerve section. Although sectioning a peripheral muscle nerve removes both sensory and motor functions for that particular muscle, such sections are useful in evaluating the capacity of cats in the intact or spinal state to adapt its locomotor pattern when specific muscles are removed. Nerves to ankle flexors (tibialis anterior, TA and extensor digitorum longus, EDL) were cut in one leg while cats had an otherwise intact spinal cord and had been chronically implanted with EMG electrodes (Carrier *et al.* 1997). Remarkably, following such a neurectomy, locomotor movements were very similar to control after only a few days. There was obviously some reduction in the ankle flexion and the amplitude of hip and knee flexor EMGs were increased to compensate for the reduced ankle flexion. When the cats had recovered a stable symmetrical locomotion they were spinalized, and walking became asymmetric and included increased hip flexions during swing on the denervated side, which were largely dysfunctional. However, when the neurectomy was performed in a spinal cat that had already recovered locomotion, there was a reduced ankle flexion but no abnormal dysfunctional hyperflexions as observed when the neurectomy was performed before spinalization. It can thus be concluded that the removal of a muscle usually active during locomotion results in plastic changes occurring both at the spinal and supraspinal levels. The spinal cord alone does not seem capable in this case to compensate functionally but there are undoubtedly changes occurring in the cord manifested as hyperflexions. How supraspinal and spinal changes combine to produce an almost normal locomotion when the neurectomy is performed before spinalization is still being investigated.

Similarly, others have developed a model of muscle neurectomy of the gastrocnemius lateralis–soleus

(GLS; Whelan *et al.* 1995; Pearson *et al.* 1999; Pearson 2000). Such a neurectomy produces a marked yield at the ankle but 5 days after, agonist muscles such as MG and plantaris compensate for the removal of GLS by increasing their discharge amplitude leading to a compensation of the yield. We used the same model for collaborative experiments (Bouyer *et al.* 2001) in which the GLS nerve was sectioned on one side in three chronic spinal cats after they had regained normal spinal locomotion (see above). Similarly to the intact state, a significant ankle yield was observed during stance for the first few days, and the GM burst of activity markedly increased. The yield almost completely recovered within a week and GM activity remained elevated. The mechanisms of such compensation in spinal cats still have to be elucidated but surely the observations clearly indicate a functional compensation in the spinal state suggesting important spinal capacity for adaptation presumably supported by changes in synaptic transmission in various pathways.

Cutaneous nerve section. Although it is generally believed that removal of cutaneous inputs by nerve section or anaesthesia does not prevent locomotion (Sherrington 1910; Engberg 1964; Forssberg *et al.* 1977; Duysens & Stein 1978; Prochazka *et al.* 1978), recent experiments on denervation of the foot pads have brought another perspective on the contribution of cutaneous inputs to locomotion (Bouyer & Rossignol 1998, 2001, 2003a,b; Rossignol *et al.* 2002). The five cutaneous nerves of the hindfeet were cut in otherwise intact cats. Within 2 days, these cats walked almost normally on the treadmill. The only detectable change was a somewhat faster swing with increased discharge amplitude of the knee and ankle flexor muscles (see figure 7). However, when placed on a horizontal ladder, soon after the foot denervation and for up to seven weeks, cats were unable to place their feet correctly on the rungs. A strategy was developed by the cats to grip the rungs and, when this capacity was achieved, the cats were then spinalized at T13.

After spinalization, cats could generate alternate walking movements of the hindlimbs but were unable to place the feet on the plantar surface, which they performed very well before spinalization even though their hindfeet had been denervated. It should also be pointed out that although ‘normal’ spinal cats (i.e. with intact cutaneous denervation) tend to drag their feet in the initial swing, this drag disappears (Barbeau & Rossignol 1987; Bélanger *et al.* 1996). We concluded from this work that on the one hand, cutaneous sensory inputs are very important for the recovery and expression of spinal locomotion. On the other hand, the functional adaptation seen after denervation in the intact state probably depends largely on supraspinal compensations since a major foot placement deficit is present after spinalization. Recent work on this model (Bouyer *et al.* 2000; Bretzner & Drew 2005a) clearly indicates that the motor cortex participates actively in this compensation. Indeed, after denervation responses to intracortical microstimulation is increased even 40 days after denervation and may contribute in setting the discharge amplitude of certain muscles such as hindlimb flexors to offset the sensory denervation (see figure 8). Also, a lesion

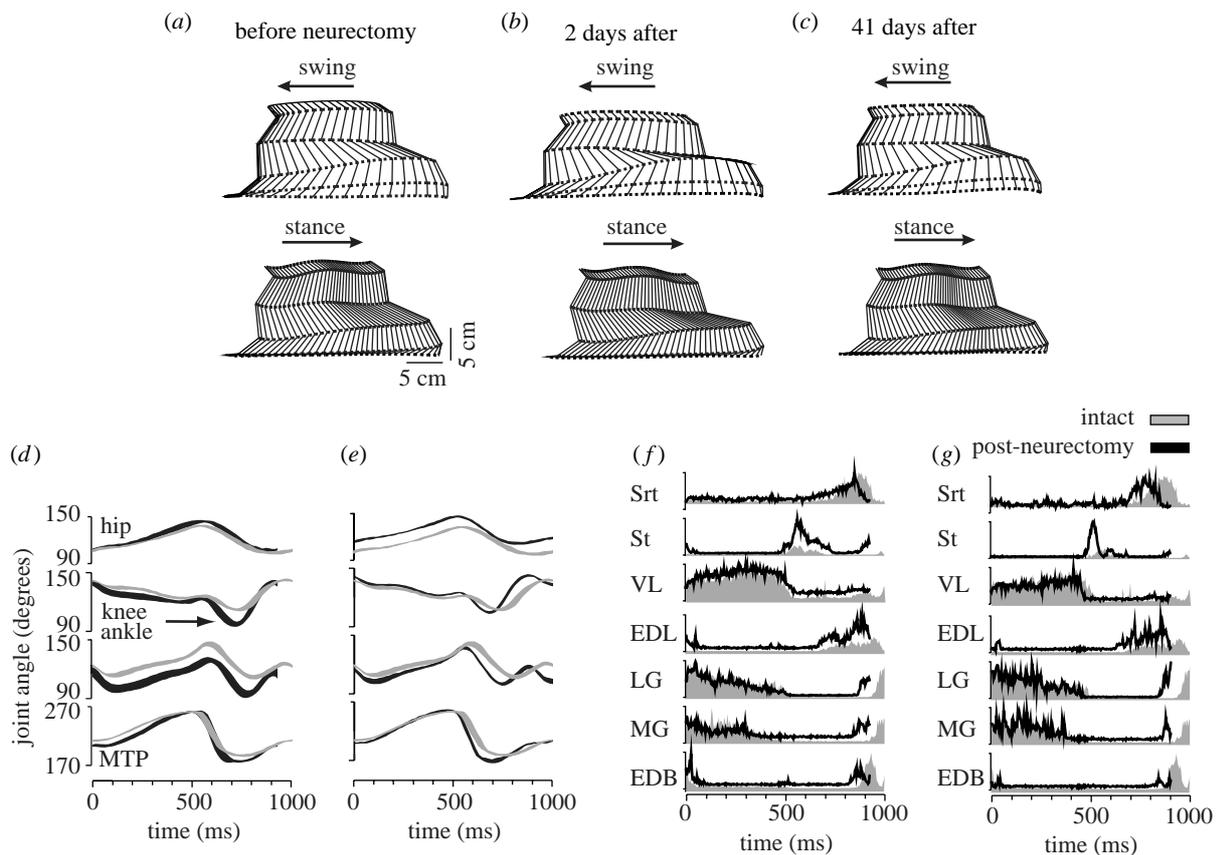


Figure 7. Cutaneous neurectomy of the hind feet in the cat. (*a–c*) Stick figure reconstructions of left hindlimb movements from a frame-by-frame video analysis of cat walking on the treadmill at  $0.5 \text{ m s}^{-1}$ . (*a*) Control, (*b*) 2 days, and (*c*) 41 days after complete denervation of both hindfeet. Horizontal and vertical scales are 5 cm. (*d* and *e*) Mean angular excursions at each of four limb joints. Thickness of lines represents 1 s.d. In (*d*), control (grey line) and 2 days postdenervation (black line) are superimposed. Dashed lines represent divisions of step cycle according to Philippson (1905) for control walking situation. In (*e*), superimposition is between control (grey line) and 41 days postdenervation (black line). Synchronization is on foot contact. Arrow highlights increased knee flexion. (*f* and *g*) Rectified averaged EMG activity of the main muscles recorded simultaneously with kinematics shown in (*d*) and (*e*). In (*f*), control EMG activity (grey area) and 2 days postdenervation (black line) are superimposed. In (*g*), superimposition is between control (grey area) and 41 days postdenervation (black line). Srt, sartorius anterior; St, semitendinosus; VL, vastus lateralis; EDL, extensor digitorum longus; LG, lateral gastrocnemius; MG, medial gastrocnemius; EDB, extensor digitorum brevis. Reproduced by permission from Bouyer & Rossignol (2003a).

of the motor cortex may disrupt the compensation seen after neurectomy (Bouyer *et al.* 2000).

Does this mean that *all* the plastic changes occur exclusively in descending pathways? Two experiments suggest that this is probably not the case. The first concerns one cat that had been completely denervated except for a tiny cutaneous branch originating from the deep peroneal nerve. This spinal cat could indeed regain a correct foot placement during locomotion, which disappeared after anaesthesia of the receptive field of that nerve or after cutting that last remaining nerve. The implication here is that the spinal cat adapted its locomotion based on considerably reduced cutaneous sensory input, suggesting an important reorganization at the spinal level itself. To address the question of spinal plasticity further, we performed a progressive cutaneous denervation of one hindfoot in a cat that had been spinalized before and had recovered locomotion. It was fascinating to see that this spinal animal could adapt its locomotion after each individual nerve section until all cutaneous nerves were cut in that hindfoot, a time at which the cat lost the ability to place the foot on the plantar surface as was the case in other cats (Bouyer & Rossignol 2003b). These experiments clearly show that

when an animal must adapt its locomotion after loss of cutaneous information that plastic changes in supraspinal and spinal connections occur.

#### (ii) Rat

Earlier sections dealt with work performed on the cat. Similar work was done on rodents but only some highlights will be given as they pertain to the main topic of this review. In fact, several other chapters in this issue deal with various types of lesioned descending pathways (CST) or spinal lesions (weight drops (Young 2002), surgical overhemisections (Bregman 1998)) in rats and the recovery of function.

The interest of partial spinal lesions is to study plastic changes leading to functional recovery. Probably the best type of work of this kind is exemplified by Bareyre *et al.* (2004) showing the development of new circuits using propriospinal neurons as relay neurons to re-establish function.

Although rats spinalized early after birth can recover locomotion (de Leon *et al.* 2002), adult rats do not recover spontaneous treadmill walking after a mid-thoracic spinalization in contrast to the situation in adult cats. However, adult chronic spinal rats can walk

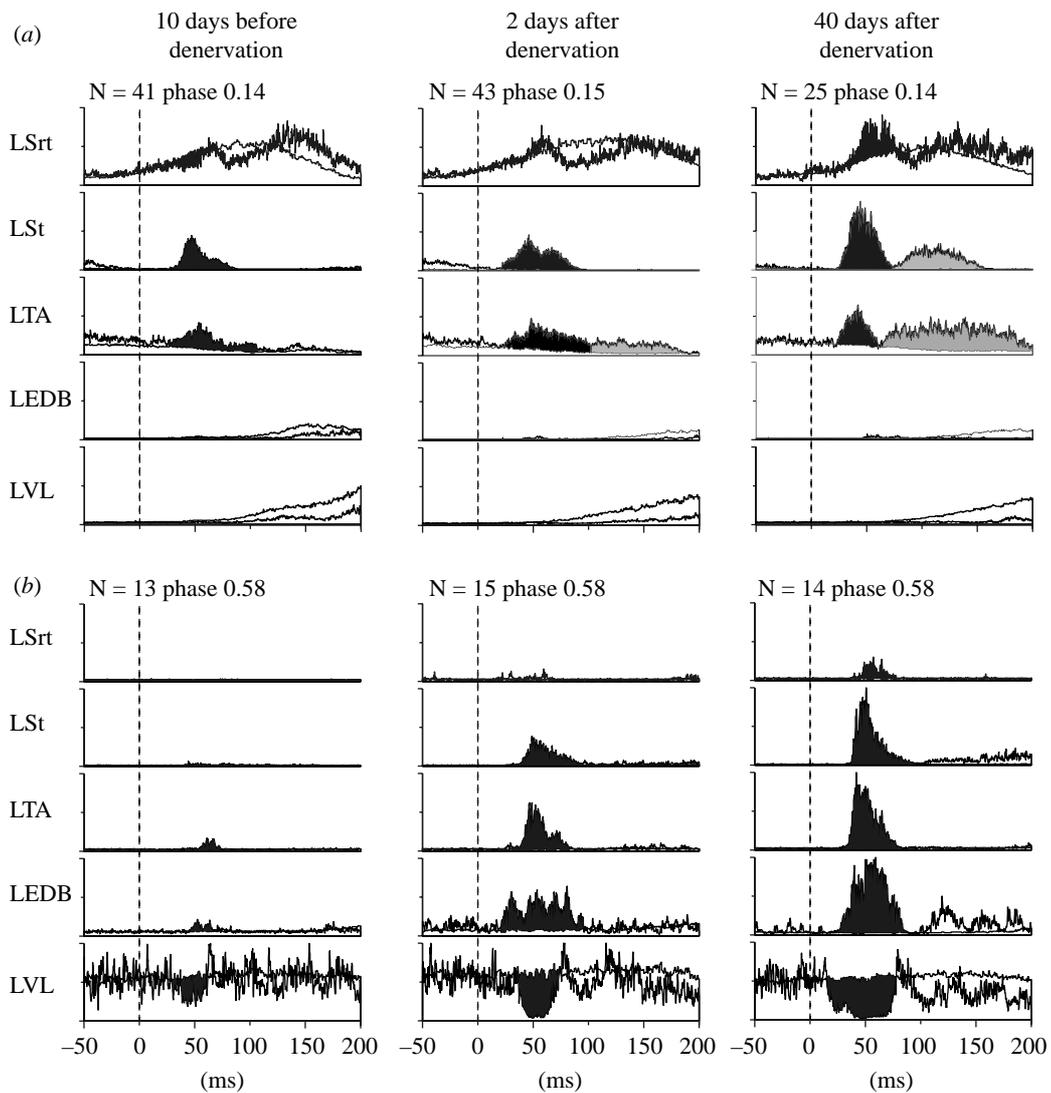


Figure 8. Increased corticospinal efficacy after a unilateral complete cutaneous denervation of the foot. (a) Average of EMG responses evoked during the swing phase at a current strength of  $35 \mu\text{A}$  before and after denervation from a microwire implanted in the motor cortex. For the St and TA, the figure identifies both short (black) and longer (grey) latency responses. (b) Average EMG responses, evoked by the same microwire at the same current strength during the stance phase. Note that the scale used to display a given EMG is constant in all traces. Note the significant increase in the muscle responses evoked by the cortical microwires even 40 days after the cutaneous denervation. Reproduced with permission from Bretzner & Drew (2005a).

on a treadmill with the hindlimbs using different forms of stimulation thus demonstrating the important capacity of the cord to generate locomotion in the rat. For example, serotonergic stimulation (Feraboli-Lohnherr *et al.* 1999) induces a locomotor pattern and chronic treatment with serotonergic agonists maintains this ability (Antri *et al.* 2002, 2003; Orsal *et al.* 2002). Recently, electrical stimulation of the dorsal columns together with 5-HT stimulation was shown to induce locomotion on a treadmill in adult spinal rats (Ichiyama *et al.* 2005).

Perhaps the most relevant work in the context of this issue is the work on transplant of mesencephalic embryonic 5-HT cells below a chronic spinal lesion performed in adult rats (Feraboli-Lohnherr *et al.* 1997; Ribotta *et al.* 2000). This showed that 5-HT cells, implanted after a spinal section, re-establish contacts with target neurons in various parts of the cord and facilitate the expression of a well-coordinated locomotor pattern. Importantly, even following a second spinal transection at T8, the locomotor capability

remains showing that the locomotor capability was not due to regeneration of axons through the lesion which could have been favoured by the graft but rather by the sublesional graft itself which acted as more or less a biological pump of 5-HT that raised the excitability of relevant spinal circuits (see figure 9).

Interestingly, the grafts had to innervate the upper lumbar levels (L1–L2), which, in the rat, are crucial levels for the expression of locomotion (Cazalets *et al.* 1995; Cazalets 2000; see earlier for critical levels in the cat at L4). Indeed, cell grafts that did not project terminals to at least L1 did not induce locomotion. Therefore, grafts at T9 (the spinalization is at T8) did not induce locomotion whereas grafts at T11 did.

Therefore, the rat spinal cord possesses the necessary circuitry to generate spinal locomotion but electrical or pharmacological stimulation, namely the serotonergic system, is required for locomotion. In that context, it is often reported that with partial lesions, there is often a regeneration of 5-HT which might explain part of the functional recovery since

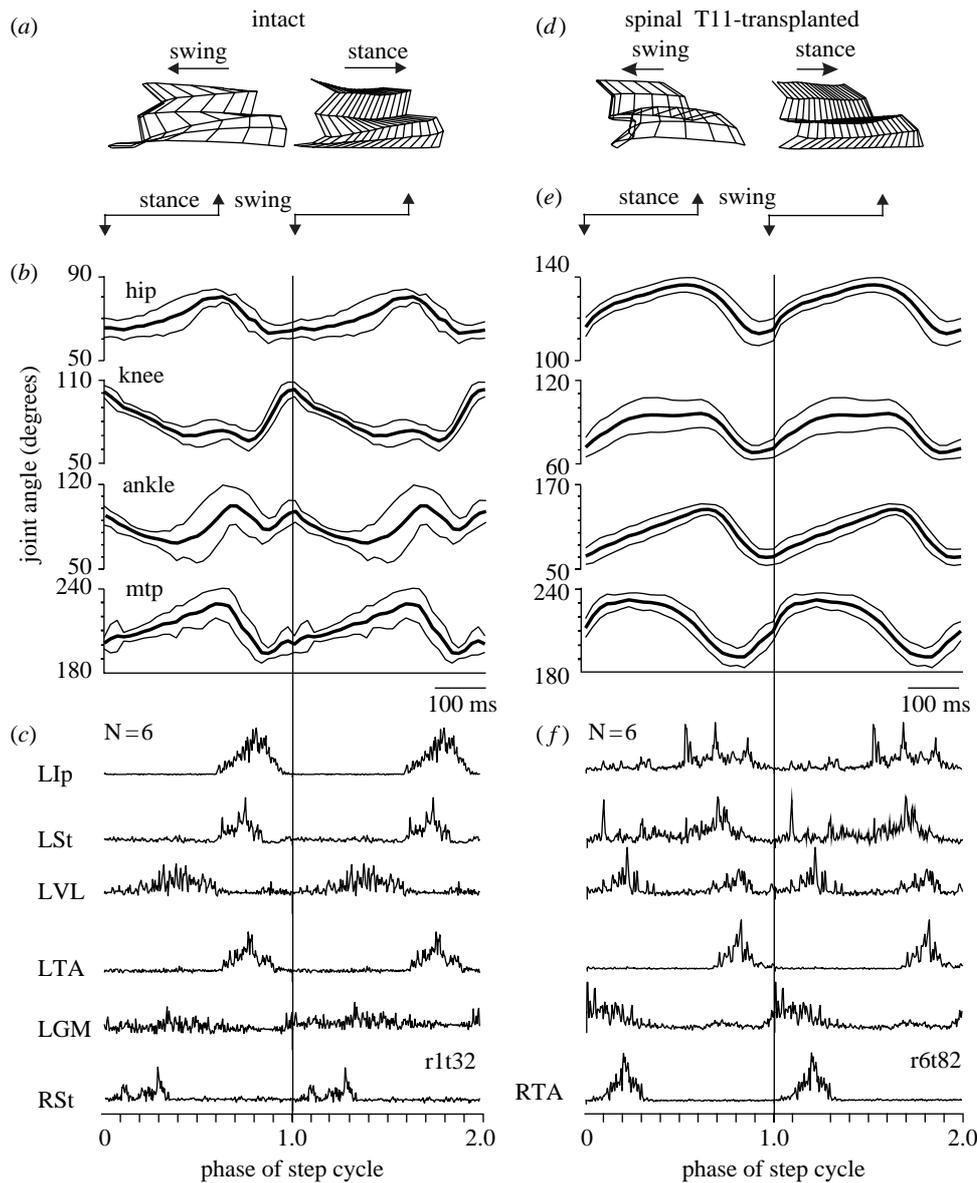


Figure 9. Comparison of rhythmic locomotor activity in an intact rat (*a–c*) and nine weeks after transplantation of embryonic raphe-cells from E14 embryos (*d–f*). (*a* and *d*) Reconstruction, as stick diagrams, of treadmill locomotor movements during swing and stance phases. Each stick figure is displaced from the previous by an amount equivalent to the foot displacement to avoid overlap of all the figures. (*b* and *e*) Variations of mean angle joints (thick lines) and their standard deviations (thin lines) from six consecutive step cycles, in (from top to bottom) hip, knee, ankle and metatarsophalangeal (mtp) joints. The same normalized step cycle is displayed twice to facilitate viewing the events at around the trigger point (foot contact of the limb facing the camera, down-going arrow). The foot lifts of the same limb are also indicated by up-going arrows. Angular excursions of various joints are averaged for six cycles and synchronized on foot contact. (*c* and *f*) Corresponding synchronized EMG activity in various muscles of ipsi (i) or contralateral (co) hindlimbs. Ip, iliopsoas (hip flexor); St, semitendinosus (knee flexor and hip extensor); VL, vastus lateralis (knee extensor); TA, tibialis anterior (ankle flexor); and GM, gastrocnemius medialis (ankle extensor). Note the discharges of LIP, LSt and LTA during the swing phase and of LVL and LGM during stance. The contralateral St (coSt) also discharges during the ipsilateral stance indicating a good alternation between limbs. Reproduced with permission from (Gimenez y Ribotta *et al.* 2000).

release of 5-HT by these axons might be sufficient to facilitate the spinal circuitry for locomotion (Coumans *et al.* 2001).

### (iii) Mouse

The adult spinal mouse is capable of hindlimb locomotion on a treadmill (Leblond *et al.* 2003) or of fictive spinal rhythms (Jiang *et al.* 1999). We have shown that the locomotor pattern can be surprisingly consistent and apparent coupling between the fore- and hindlimbs can at times be misleading but easily

detected by analysing the timing of coupling. Pharmacological work has also indicated that 5-HT agonists induce locomotion shortly after spinalization and can evoke important modulatory effects on the pattern when animals have recovered spontaneous locomotor function (Guertin *et al.* 2002; Leblond *et al.* 2002; Guertin 2004, 2005).

In models of functional recovery after partial lesions, transplants or other types of stimulation, it is very important to account for the existence of this capacity of adult mice to generate elaborate rhythmic alternate

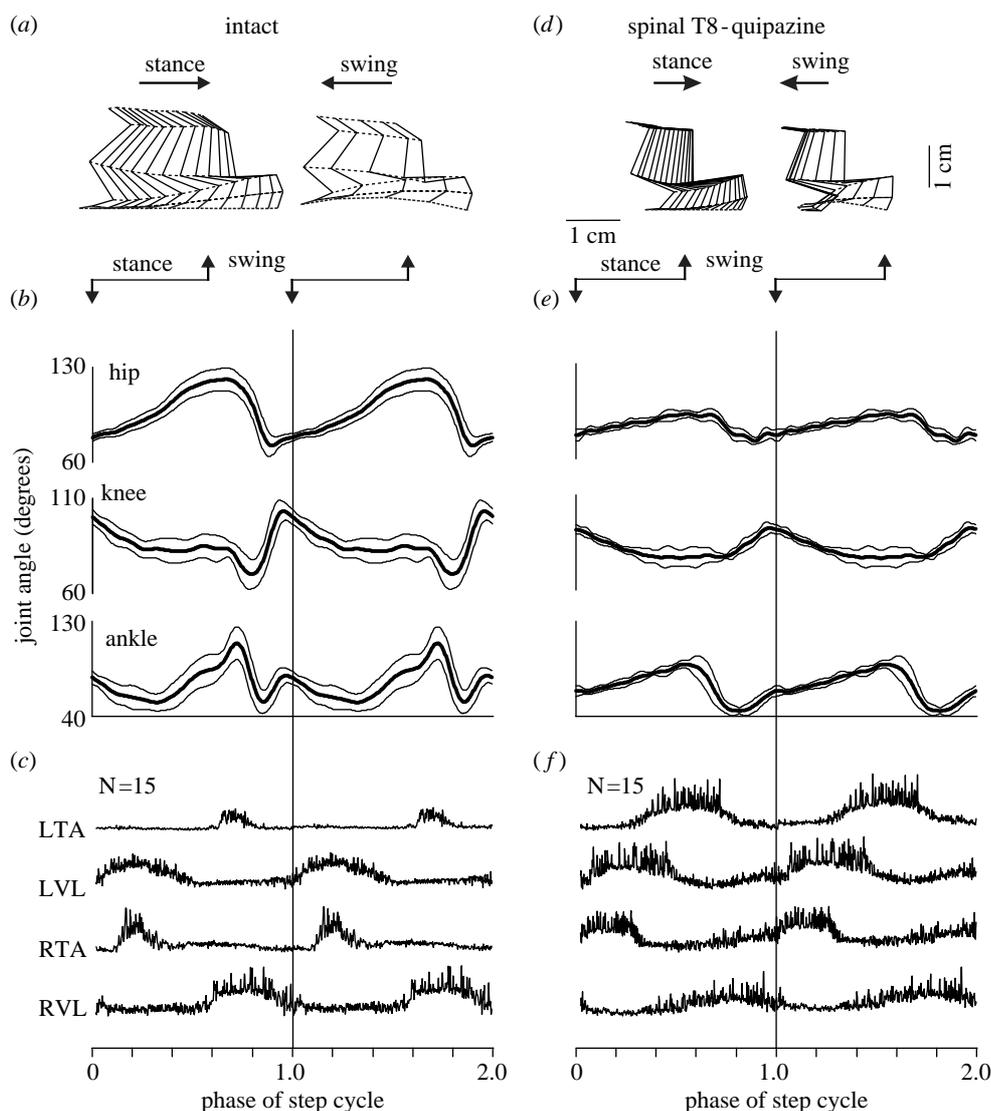


Figure 10. Comparison of locomotion in an intact mouse and a spinal mouse injected with quipazine. Kinematics and EMGs during treadmill locomotion ( $0.2 \text{ m s}^{-1}$ ) in a mouse before and 15 days after a complete section of the spinal cord at T8 level. Since this mouse was not specifically trained, quipazine ( $2 \text{ mg kg}^{-1}$ ) was given to trigger a good pattern of locomotion after spinalization. (a and d) Stick diagrams representing the left hindlimb during a complete step cycle (stance and swing) (a) before and (d) after spinalization. The horizontal arrows indicate the direction of the movement (stance and swing). (b and e) Angular excursions of three joints averaged over 15 cycles (b) before and (e) after spinalization. All angle measurements were synchronized with the left foot contact; flexions correspond to downward deflections of the traces. Downward arrows indicate foot contact and upward arrows indicate foot lift (repeated for two cycles). (c and f) EMG recordings of two flexor muscles: the left and right tibialis anterior (LTA and RTA) and two extensor muscles: left and right vastus lateralis (LVL and RVL) averaged over the same 15 cycles are rectified and normalized (c) before and (f) after spinalization.

locomotor pattern of the hindlimbs with sensory stimulation, even though it might be seen as a confounding issue to evaluate the real impact of a given treatment.

The possibility of recording kinematic and EMG (Leblond *et al.* 2003; Fong *et al.* 2005; Pearson *et al.* 2005; see figure 10) data in mice will be of great interest in view of the ongoing genetic characterization of spinal cells that might be involved in locomotion (Kiehn & Kullander 2004). Thus, it might be feasible in the future to study the connectivity of genetically identified cells in normal and spinal mice and better identify the plastic changes occurring in well-defined cells.

### (b) Studies in humans

Despite doubts expressed about the adequacy of animal models in the study of spinal injuries (Dobkin

2004), it would appear that the framework provided by animal work has been useful in conceptualizing experiments in humans and developing locomotor training strategies based on the plasticity observed in animal experiments. The field of locomotor recovery in humans after SCI has been reviewed several times (Barbeau *et al.* 1998, 1999, 2002; Barbeau & Fung 2001) and only some highlights will be reported here as they apply to the plasticity of connections in the adult. Some reviews are particularly useful to relate animal work and the clinical conditions (Barbeau & Rossignol 1994; Rossignol 2000; Harkema 2001; Dietz & Harkema 2004).

### (i) Locomotion after spinal cord injury in human subjects

There are a number of indications that the spinal cord of humans is also endowed with intrinsic

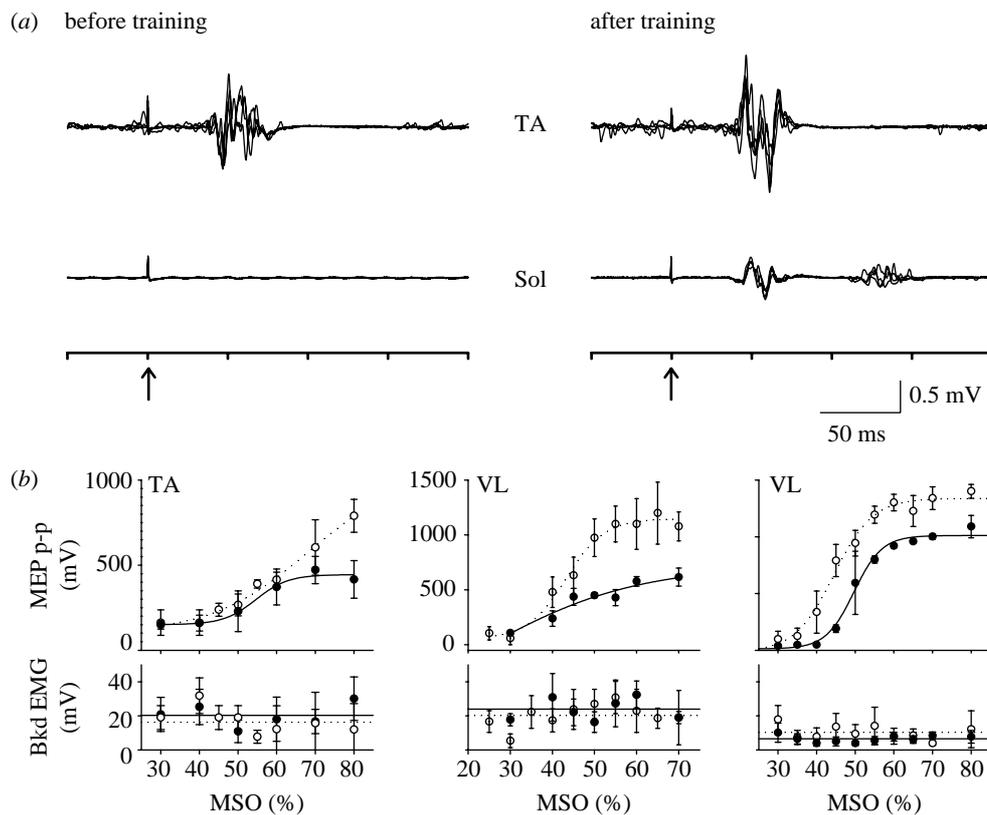


Figure 11. Change in motor evoked potentials by transcranial magnetic stimulation (TMS) in SCI patients trained on a treadmill. (a) Antagonist MEPs (four superimposed raw EMG traces) of the SOL muscle (bottom traces) to TMS while the subject (7M) produced a background contraction of the target (agonist) TA muscle (top traces). Before training (left graphs), motor-evoked potentials (MEPs) were not evoked in the electrically silent SOL muscle. After training (right graphs), the MEP in the facilitated TA muscle increased and a MEP emerged in the SOL muscle with a similar latency to that of the TA muscle (40 ms TA *versus* 41 ms SOL). Arrows mark the time of the 80% MSO (maximum stimulator output) stimulation. (b) Representative recruitment curves from three different subjects before (solid circles, solid lines) and after (open circles, dotted lines) treadmill training. Top graphs: recruitment curves from the TA (subject 5M, left graph) and VL muscles (subject 4M, middle graph; subject 1M, right graph). In all three examples, the recruitment curves after training rested above the recruitment curves before training, especially at intermediate and high stimulation intensities. The slope of the steep portion of the sigmoid line fit to the recruitment curve also increased after training although  $MEP_{\text{thresh}}$  did not change in most cases. Bottom graphs: the mean background EMG after training (dotted horizontal line) was similar to the background EMG before training (solid horizontal line). Data points represent trial mean  $\pm$  s.d. Modified and reproduced with permission from Thomas & Gorassini (2005).

capabilities to generate rhythmic movements (Kuhn 1950). With stimulation of FRAs, long latency and long duration discharges were described in SCI subjects as well as rhythmic myoclonic-like patterns (Bussel *et al.* 1988; Bussel *et al.* 1992). With epidural electrical stimulation (Dimitrijevic *et al.* 1998), rhythmic patterns could be evoked in complete SCI subjects. Whether there is in humans a central pattern generator for locomotion would require recording of such a pattern after a complete section and after curarization as was done in several species (see above) and also in non-human primates (Fedirchuk *et al.* 1998).

In humans, the term functionally complete SCI refers to the inability of the subjects to produce voluntary movements or to feel sensory stimuli. However, this might be somewhat misleading since the absence of voluntary movement does not *per se* mean that the spinal cord is anatomically completely sectioned and, therefore, all the phenomena observed after injury are due to the action of the spinal cord. However, it is likely that spinal or subcortical areas

contribute to the involuntary expression of such locomotor pattern. One spectacular case was reported (Calancie *et al.* 1994) of a functionally complete SCI subject who could generate involuntarily fairly elaborate alternating locomotor movements of the lower limbs when reclined and with the hip extended. This lasted for a prolonged period but subsided indicating that some other descending control must have taken over to suppress these unwanted movements.

It was shown that in clinically complete SCI subjects, a locomotor pattern could be generated by passive manual entrainment (Dietz 1995; Dietz *et al.* 1994, 1995) and the pattern expressed was more complete in patients with higher lesions (Dietz *et al.* 1999). These patterns are interpreted to result from interactions between a spinal cord locomotor generator and sensory afferent feedback, namely the activation of load afferents (Dietz *et al.* 1995; Harkema *et al.* 1997). On the other hand, it was shown that functionally complete spinal cord subjects could recruit more muscles and at a higher level of activity when walking with body weight support than when attempting to

produce voluntary movements (Maegele *et al.* 2002). This suggests that remnant voluntary control coupled with enhanced sensory inputs can combine to shape the locomotor pattern as is the case in animals.

#### (ii) Locomotor training

Patients with partial spinal cord lesions can walk albeit with some deficits (Pepin *et al.* 2003*a,b*). Animal and human experiments suggesting a potential for an involuntary rhythmogenesis at the spinal cord/brainstem level has encouraged the promotion of locomotor training on a treadmill with body weight support, robotics or muscle stimulation with remarkable results (Barbeau *et al.* 1987*b*; Colombo *et al.* 1998; Wernig *et al.* 1999; Behrman & Harkema 2000; Edgerton *et al.* 2001; Barbeau *et al.* 2002; Wirz *et al.* 2005). Thus, patients who were wheel-chair bound could transfer the benefit of their treadmill locomotor training to daily life situations.

#### (iii) Changes in ascending and descending pathways after lesions

This is a very large topic in itself and only very recent work on aspects relevant to the present theme is discussed.

A recent report on patients with a chronic cervical lesion of more than six months describes the emergence of interlimb reflexes coupling cervical and lumbosacral segments (Calancie *et al.* 2005). The relevance in the present context is that these interlimb reflexes are not apparent within the first six months but gradually develop, suggesting an ongoing plasticity of connections even in the adult after spinal injury.

Another very significant piece of work (Thomas & Gorassini 2005) has shown that functional locomotor improvement after 3–5 months of locomotor training in humans with SCI is accompanied by a significant change in motor potentials evoked by transcranial magnetic stimulation (TMS; see figure 11). Thus, it can be concluded that the overall transmission in the cortico-spinal pathway is enhanced by locomotor training and may, at least in part, be responsible for the functional amelioration. This could be achieved at different levels as shown for the changes occurring after neurectomies (Bretzner & Drew 2005*a,b*). In the present case, however, a change in intracortical excitability was also observed suggesting intracortical modifications of excitability resulting from locomotor training.

### 3. CONCLUDING REMARKS

This review has attempted to summarize some aspects of a very large topic dealing with plasticity of connections after spinal injury in adult mammals. The issue of locomotor recovery in animal models was addressed and the point was made that recovery is partly due to plasticity within existing spinal locomotor networks. Locomotor training appears to change the excitability of simple reflex pathways as well as more complex circuitry. Some work was reported demonstrating the potential intrinsic plasticity of the spinal cord in adapting to lesions (central or peripheral) but, usually, adaptation to lesions entails changes both at spinal and supraspinal levels. Finally, a very brief

overview of human work was given to indicate at least that the principles regulating the recovery of locomotor functions in humans are probably very similar to those observed in animal experiments.

It is comforting to think that the nervous system, even at the adult stage, is plastic enough to optimize internal motor sequences after lesion, that this can further be optimized by various types of stimulation (pharmacological, electrical) and prepares the terrain for further success in axonal regeneration to add voluntary and more refined controls of the expression of locomotion after spinal lesion.

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