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Re-expression of Locomotor Function After Partial Spinal Cord Injury

S. Rossignol,[1,2] G. Barrière,[1,2] O. Alluin,[1,2] and A. Frigon[1]

[1]Department of Physiology, Groupe de Recherche sur le Système Nerveux Central, Faculty of Medicine, Université de Montréal, Montreal, Canada; and [2]Multidisciplinary Team in Locomotor Rehabilitation after Spinal Cord Injury, Canadian Institutes of Health Research (CIHR)
serge.rossignol@umontreal.ca

After a complete spinal section, quadruped mammals (cats, rats, and mice) can generally regain hindlimb locomotion on a treadmill because the spinal cord below the lesion can express locomotion through a neural circuitry termed the central pattern generator (CPG). In this review, we propose that the spinal CPG also plays a crucial role in the locomotor recovery after incomplete spinal cord injury.

The consequences of spinal lesions are well known, namely paralysis, sensory and motor impairments, as well as autonomic dysfunctions (37). However, basic mechanisms leading to such deficits remain elusive, and a better understanding is required to design more effective treatments to promote partial or full recovery of these functions. Because of space limitations, we review here only some of the basic mechanisms that may underlie locomotor recovery after incomplete spinal cord injury (SCI) in quadrupedal mammals, particularly cats, rats, and mice, since this type of lesion is the most frequent in humans.

FIGURE 1 illustrates schematically our current understanding of the control mechanisms of locomotion. Fundamental to the understanding of locomotion is the concept of a spinal central pattern generator (CPG) (60, 107). The CPG is defined as a spinal network of neurons capable of generating a rhythmic pattern consisting of alternating activity between flexor and extensor motoneurons on the same side with reciprocal activation of homologous motoneurons in the other limb of the same girdle. In general, during walking or trotting, this network ensures that flexor motoneurons on one side are active with contralateral extensors and vice versa for extensor motoneurons. However, this pattern is not a simple alternation between flexors and extensors because each muscle has, more or less, its own bursting signature (see panel between the two joints). For instance, the knee flexor, semitendinosus (St in FIGURE 1) has two small bursts per step cycle, whereas knee (vastus lateralis; VL in FIGURE 1) and ankle (gastrocnemius lateralis; GL in FIGURE 1) extensors discharge approximately synchronously but with different discharge profiles. Other types of locomotion, such as gallop, require co-activation of homonymous muscles on both sides. Strictly speaking, the term CPG should only apply to activity generated in completely spinalized (i.e., total spinal section that removes all descending pathways from the brain stem and telencephalon) and paralysed (e.g., curarization) animals, a condition that abolishes all phasic sensory inputs associated with limb movement (61, 102). In such a preparation, rhythmic activity, evoked by injecting the noradrenaline precursor l-dihydroxyphenylalanine (L-DOPA), is recorded from peripheral muscle nerves and is termed "fictive locomotion." This rhythmic activity can only be of spinal central origin because it is generated without any descending or phasic afferent inputs.

In real-life contexts, CPG activity must be turned on and off and biased on one side or another to accomplish various goals such as starting, turning, accelerating, decelerating, and stopping. This is achieved partly by various descending pathways (more on this later), but some phylogenetically old structures, such as the reticular formation, which project abundantly to the spinal cord, play a particular role in initiating locomotion (68, 120). Indeed, electrical stimulation of a circumscribed brain stem region called the mesencephalic locomotor region (MLR), which more or less coincides with the nucleus cuneiformis ventral to the inferior colliculus, can induce locomotion of all four limbs in decerebrate animals (i.e., cortex and basal ganglia removed). Various gait patterns, such as walk, trot, and gallop, can be evoked with increasing stimulation intensity.

Other descending pathways may be more important for the ongoing control of locomotion. For instance, the motor cortex is essential for various adaptive functions associated with locomotion, such as gait modification when encountering an obstacle (41). Similarly, the vestibular system is implicated in postural adjustments during locomotion (92, 93). Other descending pathways release specific neurotransmitters, which are synthesized by cells in well defined brain stem nuclei (e.g., noradrenaline in the locus coeruleus and serotonin in the raphe and parapyramidal nuclei). These neurotransmitters exert powerful effects on the spinal circuitry and can change characteristics of the locomotor pattern (107).

After incomplete SCI, although the focus is generally on damaged or spared motor descending tracts, major ascending sensory pathways are also severed by partial SCI. Sensory inputs from the limbs also play a crucial role in structuring the step cycle so that it is adapted to the ever-changing environment. For instance, proprioceptive afferents fine tune the amplitude and timing of muscle discharge, thus defining the substructure of the step cycle, whereas exteroceptive inputs, such as cutaneous afferents, are involved in correct placement of the limbs or in overcoming

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obstacles in their paths. The importance of sensory inputs in the expression of locomotion cannot be overstated and has been the subject of a few previous reviews (50, 51, 113).

Although this review mainly deals with partial lesions, it is important to know that, after a complete spinal transection, most quadruped mammals will recover some degree of locomotor function in the limbs below the lesion (33, 108, 110, 111). Cats (112), rats (52), and mice (83) can re-express hindlimb locomotion provided the spinal cord below the complete lesion is properly stimulated, either pharmacologically or through locomotor training. After a complete spinalization, the recovery of hindlimb locomotion evidently results from the re-expression of the spinal CPG, which is facilitated by afferent inputs. In well trained chronic spinal animals, it is possible to record a fictive locomotor pattern with a tonic perineal stimulation without drug application (102), again showing the prominence of a central spinal CPG that has been rendered autonomous by previous locomotor training.

Therefore, locomotion is controlled at multiple levels of the central nervous system, and a subtle and intricate balance is established between these levels of control. This then leads to the question of how an optimal equilibrium is re-established when this exquisite balance is perturbed following lesions of the spinal cord. After partial lesions, both supraspinal and spinal mechanisms could participate in the recovery of locomotion. Traditionally, although the role played by remnant descending inputs has been emphasized, the intrinsic spinal network is now receiving more attention (8). Theoretically, remnant descending pathways could take over functions of the damaged spinal cord, relegating spinal mechanisms to a secondary role. An alternative is that remnant descending pathways promote reorganization of the spinal circuitry so that the spinal CPG plays a primary role in the recovery of locomotion after partial lesions. Although both supraspinal and spinal mechanisms are most likely involved, it is important to dissociate their respective contributions to promote different rehabilitation strategies.

In this review, we will first discuss various means of producing and evaluating partial spinal lesions in animal models as well as some of the methodology used to assess locomotion and its recovery. We will discuss different types of partial spinal lesions, focusing on remnant locomotor capacities and deficits specific to abolishing certain pathways. Finally, we will discuss recent studies that highlight some of the important spinal mechanisms putatively involved in locomotor recovery and their clinical implications.

Partial Spinal Lesions

General methodological approaches

Producing partial spinal lesions. Multiple methods for producing partial spinal lesions exist, which can cause problems in interpretation because different pathways can be severed to varying extents. One can distinguish between three large classes of methods: surgical, compressive, or neurotoxic.

With surgical approaches, a laminectomy is made, and after opening the dura matter a section of the spinal cord is made in the transverse plane at the desired vertebral level. This approach is particularly useful for lesioning tracts located dorsally (e.g., dorsal columns, corticospinal, rubrospinal) (67) or for unilateral hemisections (8, 63, 65, 79). Ventral pathways can be accessed without damaging dorsal pathways through a pedicellectomy on either side of the vertebrae (18) or through a laminectomy with a lateral approach (55).

For compressions, several devices can be used to impact the cord from the dorsal aspect by dropping calibrated weights from different heights or with impactors (see later). Other approaches use a clip with two semicircular arms to compress the cord for a desired length of time with a calibrated force. Contusions can be more reproducible than surgical transections because the mechanical devices used (impactors, weight drops, clips) can be precisely calibrated (17, 48, 69, 70, 132).

Other methods to produce partial lesions of the cord include Rose Bengal toxicity (129) or demyelination using immunological methods (85, 86). Although these methods may produce more focused lesions, valuable in assessing the role of specific pathways, they do not produce the mechanical damages typical of compression or surgical injuries in which the initial lesion may progress significantly as a result of various secondary mechanisms such as neurotoxicity (125).

It is important to document the extent of the lesion as thoroughly as possible (18). Although lesions are generally assessed using histological methods (35, 59), new approaches using magnetic resonance imaging (MRI) can also evaluate damages to the spinal cord noninvasively in vivo. This is a great asset when dealing with chronic spinal lesions because one can get a fairly good approximation of lesion extent before the terminal histological evaluation. Diffusion weighted imaging (DWI), best known as diffusion tensor imaging (DTI), evaluates diffusion of water molecules through the spinal cord and the isotropy/anisotropy of diffusion along white matter tracts. By connecting the main eigenvectors of successive voxels, the tensors delineate the white matter continuity in various parts of the spinal cord from various seed points in different quadrants, a process called tractography (25). The problem with DTI is that it represents the main vector of diffusion. Other related methods (HARDI for high angular resolution diffusion imaging) such as Q-ball imaging could identify the course of fiber tracts in different directions (26), a potentially very useful feature to detect reconfiguration of pathways around the SCI. Functional MRI (fMRI) could also be used eventually to detect functional changes in the spinal cord following injury. However, the BOLD (blood oxygenation

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level detection) signal in the cord is still problematic for various reasons (27), namely that the BOLD response is based on the hemodynamic response, which is delayed by several seconds relative to neural activity. Other methods may also be applied based on different principles (123).

Evaluating Locomotor Performance

Evaluating locomotor performance is crucial to assess the degree and quality of locomotor recovery after SCI. Some methods are useful to give an overall assessment of locomotor behavior, such as the BBB score (21 points score). The BBB assesses various aspects of locomotion such as foot placement, weight bearing, and interlimb coordination (11). This method, however, more or less assumes a linear recovery of locomotion, which might not be realistic. For instance, depending on lesion extent, forelimb-hindlimb coordination can be permanently lost, resulting in a maximal score of 12 that will not reflect further improvements of hindlimb locomotor capacities (3, 108). However there is a correlation between the size of the lesion produced by a contusion and sensorimotor deficits that may follow a high-order polynomial (77). Other methods evaluate some skilled aspects of locomotion, such as the ability to place the foot on a horizontal ladder or the capacity of animals to grip a turning rod (Rotarod). These methods are useful to evaluate the voluntary control of locomotion of all four limbs (49, 80, 94).

Finally, the most objective and accurate method to evaluate the locomotor pattern is by using chronic electromyography recordings combined with synchronized video recordings of movementjs (14). Although more cumbersome and resource intensive, this method permits a powerful quantitative comparison between locomotion observed before and after a spinal lesion, as well as its evolution over time (8) (see FIGURE 2).

Specific partial spinal lesions

Lesions of specific quadrants will first be detailed with respect to their consequences on locomotion, emphasizing remaining capabilities and deficits. We will then review unilateral hemisection studies, which lesion simultaneously dorsal and ventral quadrants on one side and compressive lesions, which incompletely damage several spinal tracts. FIGURE 3 summarizes the location of the main descending pathways in the spinal cord of the cat, as determined from previous work (64, 105).

Dorsal-dorsolateral lesions. Following unilateral or bilateral lesions to the dorsal-/dorsolateral spinal cord, which contains ascending sensory pathways and descending motor pathways, such as the corticospinal (CST) and rubrospinal (RST) tracts (81), animals can eventually recover a voluntary quadrupedal locomotion. It should be recalled that the CST in cats is dorsolateral, whereas it is just ventral to the dorsal column in the rat. Although past studies showed that lesioning the dorsal/dorsolateral spinal cord produce only transient deficits in overground or treadmill locomotion (46, 57), more detailed analyses demonstrated that, even during "simple" locomotion, persistent deficits arise (67, 73, 96). In cats, early after a bilateral dorsal/dorsolateral lesion at T13, the most consistent deficits are dragging of the hindpaw along the treadmill belt at swing onset due to impaired intralimb coupling between hip and knee joints at the stance-to-swing transition (67). In cats and rats, dorsal/dorsolateral spinal lesions

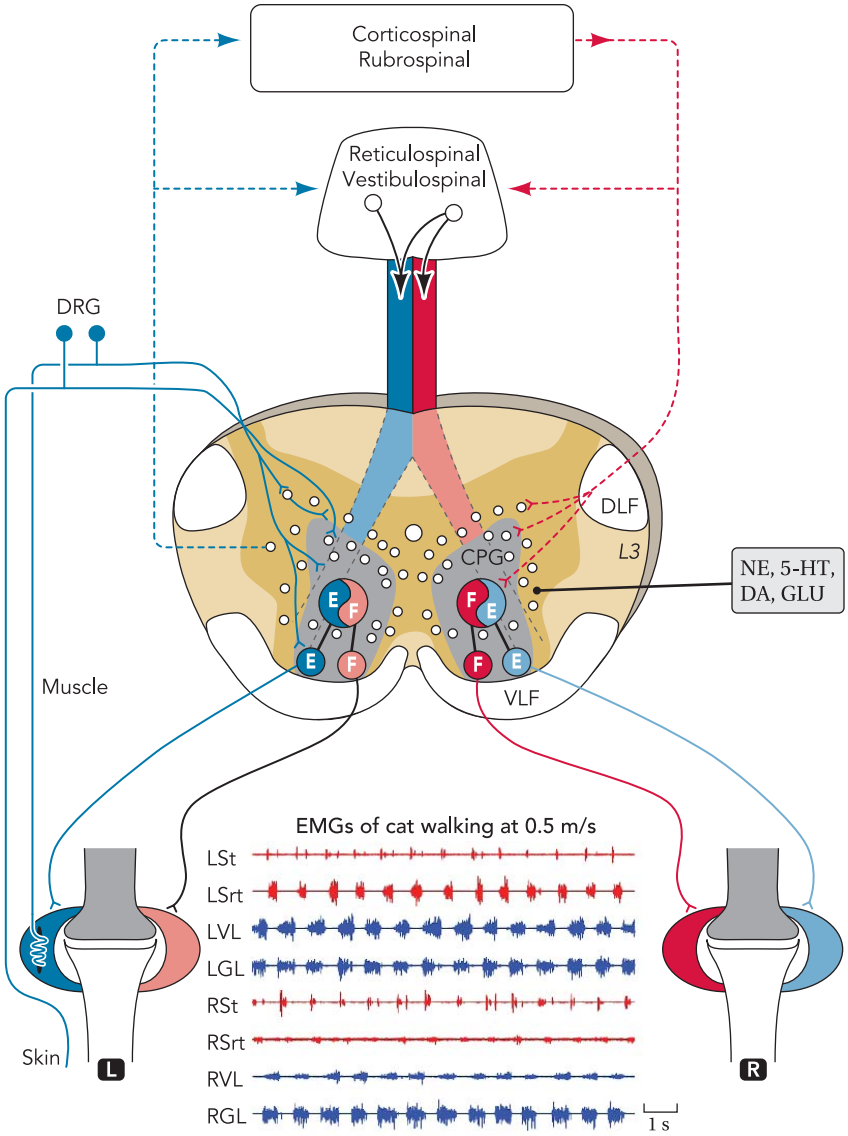

FIGURE 1. **General scheme of locomotor control (107)**
At the center, the spinal cord contains a network of interneurons capable of generating the basic locomotor pattern of flexor (St-Semitendinosus; Srt, Sartorius) and extensor motoneurons (VL, vastus lateralis; GL, gastrocnemius lateralis) on both sides (L, left; R, right) (the spinal central patten generator or CPG) (60). Various descending pathways act directly on the spinal cord or through the reticular formation to initiate or modulate the locomotor pattern for goal-directed behaviors. These supraspinal inputs are carried through the dorsolateral funiculus (DLF) or the ventrolateral funiculus (VLF). Neurotransmitters such noradrenaline (NE), serotonine (5-HT), dopamine (DA), or glutamate may also affect the properties of the CPG. Afferent inputs from the skin and muscles (cell bodies in the dorsal root ganglia or DRG) also contribute to the step-by-step adjustments of the cycle (113).

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impair the coordination between the fore- and hindlimbs (i.e., interlimb coordination) but not the coupling between homologous limb pairs (47, 56, 67).

The main component of the CST does not appear to be critical for the control of locomotion in cats or rats because unilateral or bilateral lesions of the CST at the pyramidal level do not produce long-lasting deficits in overground or treadmill locomotion (46, 97). On the other hand, sectioning other dorsal/dorsolateral pathways, such as the RST and ascending sensory pathways (ASPs), produces persistent deficits during overground and skilled locomotion in the rat. For example, a unilateral dorsolateral funiculus (DLF), dorsal funiculus (DF), or combined DLF/DF lesion at C3 produces clear persistent ipsilateral (i.e., ipsilateral to lesion) forelimb and hindlimb deficits during overground locomotion, mainly in the ability to generate ground reaction forces (130). Skilled locomotion, assessed by a horizontal ladder walking test, is also impaired with increased paw placement errors in the fore- and hindlimbs. Deficits are similar to those observed following unilateral ablation of the red nucleus (98), indicating an important role of the RST in regulating flexor and extensor activity during overground and skilled locomotion. Large lesions of the dorsal spinal cord in rats will even abolish the capacity for skilled locomotion (73).

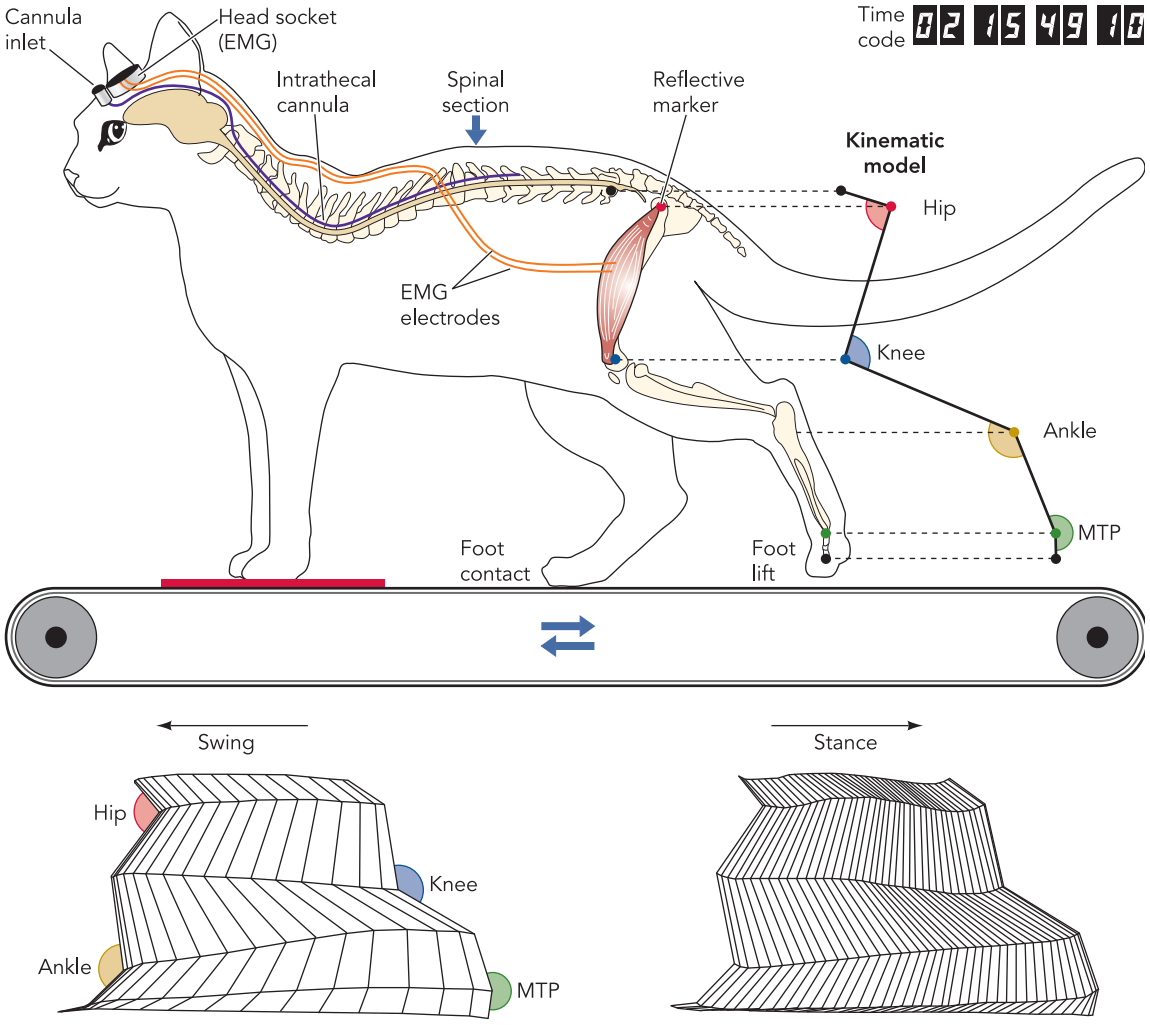

FIGURE 2. **General methodology for the study of locomotion in cats with spinal lesions**
Initially, the animal is placed with its forelimbs standing on a stationary platform while its hindlimbs walk on the treadmill (arrows within the belt indicate the direction of movement). Later on, cats can walk freely on the treadmill with all four limbs. Pairs of EMG wires are implanted into various muscles (only 1 pair is represented here), and an intrathecal cannula is inserted through the atlanto-occipital ligament down to ~L4. The multi-pin EMG connector, as well as the cannula inlet, are cemented to the skull. Reflective markers are placed at various points on the limb, and the angle measurements are taken in the indicated orientations. For each video field (16.7 ms between fields), the coordinates of the reflective markers are obtained, and the hindlimb movement is reconstructed as indicated in the kinematic model (MTP = metatarsophalangeal joint). From such data, the swing and stance phases of each cycle can be reconstructed as shown below. Note that, to prevent overlap of the stick figures, each one is displaced by an amount equal to the displacement of the foot along the horizontal axis. The foot contact and foot lift are also measured to determine cycle length and duration and also to synchronize EMG events when needed. The digital (SMPTE) time code (*top right*) is used to synchronize video and EMG recordings. The spinal lesions are made at T13, unless otherwise specified.

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Deficits stemming from DLF and/or DF lesions do not solely stem from RST damage. Ascending sensory pathways in the DF are important in regulating muscle activity during locomotion because selective DF lesions that spare the main CST and RST produce deficits similar to DLF lesions (73). Moreover, ascending sensory pathways appear particularly important for functional recovery after RST damage because abolishing these pathways in the DF after bilateral DLF lesions severely impaired recovered skilled locomotion (73).

What emerges from these studies is that descending and ascending pathways in the dorsal/dorsolateral spinal cord are normally involved in overground locomotion and become increasingly important during skilled locomotion. The RST appears relatively more important for hindlimb locomotion in quadruped mammals than the CST because RST lesions produce long-lasting deficits, whereas, following selective lesions of the main component of the CST in cats (46) and rats (97), animals make a full recovery. Although there is no direct evidence, locomotor recovery following CST lesions could be due to "functional substitution" by the RST (67), whereas the CST appears limited in substituting for the RST.

Therefore, lesions of the dorsal/dorsolateral produce initial deficits that gradually recover, particularly during treadmill or overground locomotion, and some deficits that persist, which are more apparent during skilled locomotion. Both descending and ascending pathways appear to participate in locomotor recovery.

Ventral-ventrolateral. Ventral spinal lesions have attracted considerable interest because some of the main descending pathways, such as reticulospinal and vestibulospinal pathways are located ventrally. Given that stimulation of the MLR activates reticulospinal pathways (100, 101, 119), it is natural to presume that lesions of these pathways through ventral spinal lesions will result in severe paralysis. Several lesion studies were performed in rats and cats (1, 54, 55). In the rat, locomotion can be re-instated, provided that part of the ventral pathways remains. However, in the cat, although complete ventral lesions (performed through a pedicellectomy) result in the abolition of voluntary hindlimb locomotion for 3–4 wk, locomotion does return, albeit with some deficits, such as fore-/hindlimb coordination and some weight-support deficits leading to occasional stumbling (18, 19). However, the intralimb locomotor pattern of the hindlimbs is well preserved. Cats also develop a strategy whereby weight support is largely shifted toward the forelimbs, contrary to the case in normal cats. The development of such compensatory strategies is important in the context of locomotor recovery. Similar compensatory strategies involving cervical segments are also found in humans with SCI (58).

Besides its role in triggering locomotion, the reticulospinal pathways are also implicated in the step-by-step control of locomotion. Given their widespread projections, these cells may participate in the coordination between limbs as well as in weight support directly or as an integrative relay between the cortex and spinal cord (39, 42, 43, 71, 72, 103, 104, 116). Similarly, vestibulospinal pathways affected by these lesions normally have an important role in postural control during locomotion (92, 93).

Hemisections. In contrast to bilateral lesions of the dorsal/dorsolateral or ventral/ventrolateral spinal cord, unilateral hemisections completely damage ventral and dorsal tracts on one side only, with primarily incomplete damage on the other side. Following such lesions in rodents, cats, and monkeys, treadmill and overground locomotion resumes within days or weeks, depending on the extent and level of the lesion (8, 15, 30, 31, 62, 63, 74, 75, 78, 115, 124). Lesion extent and the amount of locomotor training are the most important factors governing locomotor recovery and performance (e.g., maximal walking speed and endurance) (77). For instance, we recently showed in cats hemisected at the thoracic level that the smaller the lesion the faster the locomotor recovery (8). In the same study, we showed that untrained cats eventually re-expressed a quadruped locomotion but with lesser capacities compared with trained animals with similar lesions.

In cats, during the first few days after hemisection, the hindlimb ipsilateral to the lesion exhibits flaccid paresis and drags on the treadmill. At this stage, animals walk tripedally and need assistance for hindquarter support and body equilibrium during locomotion (8, 63). Within 2 wk, cats recover

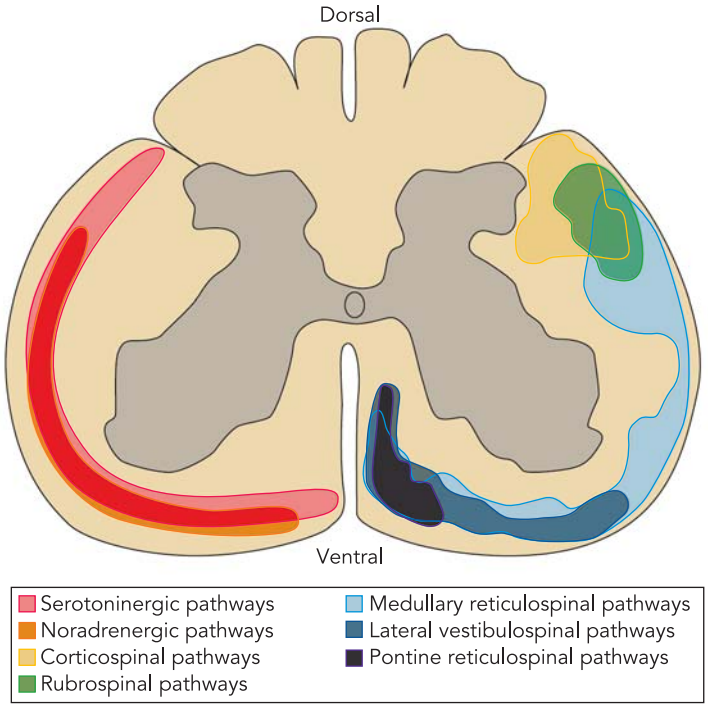

FIGURE 3. **Descending pathways in the cat as determined from the work of Refs. 64, 105**

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hindquarter support, and use of the affected hindlimb progresses from a passive crutch with minimal limb excursion to an active locomotor pattern (63, 78). The hindlimb on the lesioned side exhibits an increased swing phase duration and reduced support time that is not observed on the contralateral side. Increased swing duration is, however, marked by a limited limb excursion that results in foot contact behind or just below the hip joint. During swing, an important paw drag is commonly observed and stance is performed on the dorsum of the hindpaw. The swing-to-stance transition on the lesioned side is marked by excessive abduction of the hindlimb and is initiated with a more extended hip position compared with the intact side (8, 63, 78). Interlimb coordination between fore- and hindlimbs is also affected (8, 15, 63, 78). With large lesions, an uncoupling of the fore- and hindlimbs is observed and the cycle frequency is respectively increased and decreased in the fore- and hindlimbs. With smaller lesions, coupling is preserved, but a

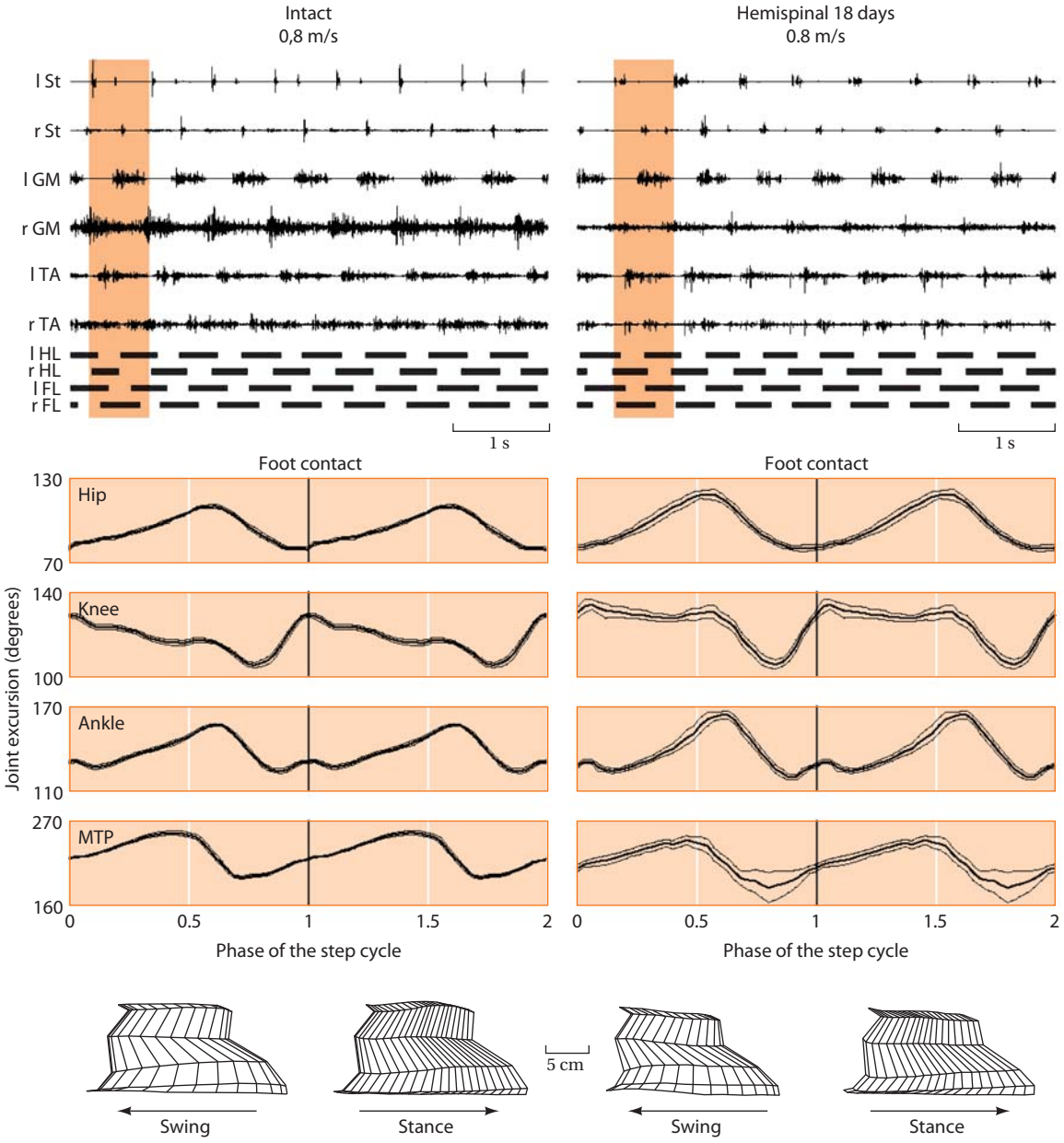

FIGURE 4. **Recovery of quadrupedal locomotion following a unilateral dorsal/dorsolateral low thoracic lesion in a cat**

Left: a sequence of treadmill locomotion before spinalization (i.e., in the intact state) at 0.8 m/s. *Top*: the EMGs were recorded in both hindlimbs and are presented with stance phase duty cycles (black bars) in the four limbs. *Middle*: mean angular excursions of the hip, knee, ankle and metatarsophalangeal (MTP) joints of the left hindlimb. *Bottom*: stick diagrams represent stance and swing phase extracted from the same sequence as the EMGs. *Right*: EMGs, mean angular excursion, and stick diagrams obtained in the same cat, at the same treadmill speed, 18 days following a unilateral dorsal/dorsolateral lesion of the spinal cord at a low thoracic level (T11). It is worth noting that this cat was trained daily following the lesion, which resulted in a similar pattern of locomotor activity compared with the intact state. l, Left; r, right; St, semitendinosus; GM, medial gastrocnemius; TA, tibialis anterior; HL, hindlimb; FL, forelimb.

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pacing activity, in which locomotor movements of homolateral limbs are synchronized, is often observed. This is often seen with spinal lesions and might correspond to a tripod gait, providing a more stable pattern of locomotion (18).

Over time and/or with training, the affected hindlimb exhibits less paw drag during swing, plantar paw placement during stance develops, and the animal can adapt its locomotor pattern to increasing treadmill speed. As a result, a symmetrical gait with proper left/right alternation is restored. However, forelimb/hindlimb coordination remains modified. In cats with small lesions, a 1:1 coupling is most often preserved, but homolateral limbs tend to walk in phase (pacing pattern), whereas in cats with larger lesions a complete uncoupling is maintained over time, the step cycle frequency being different at both girdles. Moreover, skilled locomotion, such as ladder or grid walking is also impaired following spinal hemisection (62, 63, 124). For instance, precise placement of the hindpaw on the rungs of a ladder is durably altered on the side of the lesion, and during overground locomotion the affected hindlimb cannot anticipate encountered obstacles (40).

Therefore, substantial recovery of hindlimb locomotion is observed following lateral hemisection of the spinal cord. Initial and persistent deficits are mostly observed on the side of the lesion and reflect deficits associated with ventral (transiently impaired body equilibrium) and dorsal lesions (impaired skilled locomotion).

FIGURE 4 illustrates the pattern of EMG discharge and the kinematics before and 18 days after a spinal hemilesion on the left side. The similarity of the locomotor pattern is striking, although the post-lesional pattern is somewhat more variable (see standard deviation in angular joint displacements).

Spinal contusions. The majority of SCIs in humans results from an impact to the vertebral column, which produces contusions of the spinal cord. In animals, contusion models have helped our understanding of biological mechanisms involved in the secondary injury that follows the initial SCI (121, 132). Contrary to transection models, contusive lesions are diffuse (24) and generally result in a central cavitation rimed by spared white matter (94, 106). Generally, locomotor recovery correlates with the cavitation volume and lesion severity (106). The extent of spinal white matter damage, depending on the intensity of the injury, is strongly related with the number, localization, and amount of damaged spinal tracts and thus with locomotor deficits (84, 90, 117). On the other hand, the quantity of gray matter lost after contusion poorly correlates with locomotor deficits (88).

The contusion level has a direct bearing on locomotor recovery. For instance, in rats, a contusion at T13-L2 results in greater loss of locomotor function, as assessed by the BBB scale (i.e., absence of coordination and occasional weight support during stepping), compared with the same injury at L3–L4 (88). Contusion at T13–L2 could damage key elements of the spinal CPG for hindlimb locomotion thought to be localized at L1–L2 in the rat (16, 22, 89). In a recent study, the effects of training on electrophysiological properties were studied in different groups of rats 1 mo after compression of the thoracic spinal cord (12). Stimulation of the ventrolateral funiculus at C5 generated extracellular field potentials at L3, and it was shown that neuronal conductivity was severely impaired in untrained rats compared with trained rats, although in both injured groups it remained much below that of uninjured controls. These data indicate that training can restore some of the connectivity between cervical and lumbar levels. The authors attributed a role of brain-derived neurotrophic factor (BDNF) because trained injured rats showed elevated levels of BDNF compared with the untrained group (12). Others have also demonstrated increased levels of BDNF in monkeys after partial spinal lesions (134). Electrophysiological changes were associated with a decreased capability to lift and advance the hindlimbs (28), producing an increased stance phase duration (12). Forelimb stance duration was also increased after contusion at L2 (29), which suggests a strategy to adapt forelimb velocity with impaired hindlimb movements.

With contusion injuries, lesion severity and consequently locomotor deficits can be graded according to the distance travelled by the impact device (77, 87). For example, in mice, forelimb-hindlimb coordination deficits appear after low-intensity contusion (i.e., 0.3-mm distance of impact over 23-ms period), which disappear within 2 wk post-injury, although foot placement, assessed by a grid walking test, remains deficient (87). A moderate thoracic contusion (i.e., 0.5-mm distance of impact over 23-ms period) produces immediate hindlimb paralysis followed by gradual recovery of plantar stepping, although poor forelimb-hindlimb coordination remains. Moreover, mice with moderate contusions exhibit persistent paw drag, paw rotation, and loss of coordination between fore- and hindlimbs. With severe contusion (i.e., 0.8-mm distance of impact over 23-ms period), mice show flaccid paralysis during the first week post-injury and gradually recover small joint movements, but voluntary locomotion with full weight support does not recover (87). After contusion injury, locomotor training (99, 127, 128) and afferent inputs from the periphery appear to play an important role in the recovery process (122).

Therefore, locomotor capabilities after spinal contusion depend on lesion severity and activity-dependent processes, such as locomotor training (99, 122).

Compensatory Mechanisms Leading to the Re-expression of Locomotion

The above summary on partial spinal lesions emphasizes how lesions of various pathways can induce

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variable deficits that affect step length, step frequency, interlimb or intralimb joint coupling, foot drag, or deficits in weight support. What is remarkable is how the CNS optimizes locomotion through the action of remnant structures.

Following partial spinal lesions, the voluntary recovery of locomotion undoubtedly reflects changes in sensorimotor interactions within and between the spinal CPG, descending supraspinal and propriospinal inputs, as well as peripheral sensory feedback (109). In cats, after partial or complete spinal lesions, the re-expression of locomotion is facilitated with treadmill locomotor training and by stimulating the skin of the perineal region (5, 8). Whereas perineal stimulation provides a more or less tonic cutaneous input, locomotor training provides phasic cutaneous and proprioceptive feedback that is consistent with normal locomotion. These sensory cues are thought to promote reorganization of the spinal locomotor CPG so that it can operate more efficiently with diminished influences from supraspinal structures (44, 113). Descending motor pathways are also altered following incomplete SCI and, through activity-dependent processes, can induce changes within spinal sensorimotor pathways (23, 126). Compensatory changes within the central nervous system after incomplete SCI no doubt involve several mechanisms, such as sprouting, regeneration, and functional synaptic modifications.

Thus, although there are some specific deficits due to the inactivation of specific functional pathways, animals can in most instances eventually regain a functional locomotor pattern, enabling them to move around even in the open field. Several mechanisms probably participate in the functional recovery of locomotion, and none are mutually exclusive. We will review some of these mechanisms and propose that physiological, and most likely anatomical, plasticity at the spinal level below the injury participates in an important manner in the re-expression of locomotion after partial SCI.

Sprouting and regeneration

Work aimed at blocking molecules (e.g., anti-NOGO, anti-Rho) that hinder regeneration shows fiber growth through or around the spinal lesion. However, these fibers, which may partly originate from regenerating damaged or sprouting undamaged fibers, only reach a few millimeters below the lesion (7). On the other hand, 5-HT fibers can grow for longer distances and, as such, change the local excitability of the spinal circuitry below the lesion. Moreover, what is unclear is whether increased sprouting and/or regeneration leads to improved functional outcomes or maladaptive changes within the spinal cord.

It was shown that, following lesions of descending pathways, new circuits could be formed by sprouting of remaining descending fibers that eventually reach the spinal cord via new routes, including propriospinal neurons (7). This is the case after lesioning the CST, in which collaterals reach cell bodies at the origin of other descending pathways (rubrospinal, reticulospinal, propriospinal). This raises the important issue as to whether this represents a new circuitry or the strengthening of an existing circuitry. Recent work in the in vitro neonatal rat preparation (32, 133) has shown, using a combination of serial hemisections and pharmacological stimulation, that propriospinal neurons can not only transmit command signals from the brain stem to initiate rhythmic locomotor-like activity in the lumbar cord but that they may also be sufficient. Similar conclusions were reached in the mouse (31) and in the rat (59). In a similar vein, Kato, using double hemisections in the cat (74), showed that, following interruption of descending pathways through staggered hemilesions at different levels, animals still regained voluntary locomotion, suggesting that descending commands reach the lumbar spinal cord through a system of interconnecting propriospinal neurons that form a link from the brain stem to the lumbar cord. This overall scheme of activation of the spinal locomotor CPG by brain stem stimulation was previously proposed (118).

A number of observations from our laboratory and others suggest that this propriospinal circuitry may be distributed over a certain number of spinal segments but that premotoneuronal thoraco-lumbar segments exert a powerful effect on the lumbar circuitry. In the neonatal rat, it was suggested that low thoracic and upper lumbar segments are critical for the expression of locomotion evoked through chemical simulation (22). These regions also correspond to regions of higher excitability for rhythmogenesis in the rat (76). Furthermore, excitotoxic destruction of interneurons at L2 in the rat abolishes locomotion. Inactivation of L3–L4 segments using the noradrenergic blocker yohimbine completely blocked locomotion in completely spinal cats (91). Similarly, electrical microstimulation of the spinal cord can induce locomotion in completely spinal cats, provided the integrity of these midlumbar spinal segments is preserved (9, 10). Chronic spinal cats that recovered locomotion after a first complete section at T13 will be unable to walk after a second section at caudal L3–L4 even after weeks of trying to train the animals to walk. This is not a consequence of abolishing all motononeuron activity since other rhythmic patterns can be evoked such as fast paw shakes (82). Very recent data also suggest, using injections along the spinal cord, that spontaneous decerebrate locomotion in the cat is abolished by inactivating L3–L4 segments specifically (34). None of the other segments rostral to L3–L4 could block locomotion, although the simultaneous inactivation of several segments eventually abolished locomotion. These data suggest that propriospinal interneurons mainly located

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above L4 (thus mainly hindlimb premotoneuronal segments) are essential for locomotion. The interest here is of course that, if some segments of the spinal cord have an important role in rhythmogenesis, then targeting these regions with various types of stimulation may prove to be a useful strategy because it would limit the problem to a more circumscribed area of the cord (see also Ref. 52).

How spinal locomotor circuits are activated by descending commands is of course at the heart of the problem with regard to the re-expression of locomotion after partial SCI. Lesion studies reported above suggest that, whatever the lesion, animals can usually re-express locomotion with time, albeit with some specific motor deficits. Therefore, it is important to distinguish clearly how the spinal locomotor rhythm is generated from how it is controlled. Indeed, animals may walk with some interlimb coordination deficits, weight support weakness, or foot drag, but they will walk. The bulk of the evidence suggests that multiple pathways can access the spinal network necessary for expressing locomotion. This is also the conclusion of studies indicating that the relationship between the amount of spared white matter and locomotor recovery is not linear but follows some higher harmonic function (77).

How should one envisage the role of these new or reconfigured pathways? One tacit hypothesis is that these plastic neuroanatomical changes lead to a "takeover" by descending pathways of lost spinal function. This could be achieved either by new anatomical circuits or by physiological alteration of synaptic strength of existing pathways. However, another interpretation posits that the role of remnant descending pathways after partial SCI is to regain access to and reorganize the spinal CPG so that it is optimized to perform in the absence of descending pathways. In such a model, the amount of spared white matter may not be so relevant because hindlimb locomotion is then primarily generated by the CPG. This interpretation requires showing that here is a change in the behavior of the CPG after a partial spinal lesion, which is discussed next.

The role of the spinal CPG

In experiments of spinal hemisection (T10–T11) in cats (8), it was found that cats trained to walk on the treadmill for several weeks until they regained good quadrupedal walking could also walk bipedally with the hindlimbs within hours of a complete spinal section at T13. FIGURE 5 summarizes the results of these experiments. This is a striking result because, normally, complete spinal cats require weeks to regain proper hindlimb locomotion after a complete spinal section. Our interpretation is that the spinal cord was dramatically changed during the period of locomotor recovery after the partial lesion, undoubtedly through interactions between spinal sensorimotor mechanisms and remaining descending pathways. Therefore, after a partial lesion, the expression of locomotion probably results from a combination of plastic changes (physiological and/or anatomical) within descending pathways, as well as important changes within the spinal cord. Instead of taking over lost spinal functions, remnant descending pathways or regenerating pathways could direct the reorganization of the spinal circuitry so that it can function optimally and with a greater level of independence so that, after the complete section, the full pattern of hindlimb locomotion can be expressed by an already autonomous CPG. We are currently evaluating the nature of these changes at the spinal level and the importance of the delay between the partial and complete spinal lesions in the dual lesion paradigm, as well as the importance of locomotor training in inducing these changes at the spinal level. As an example, our laboratory's previous work on complete spinal cats clearly showed an upregulation of several receptors (i.e., 5-HT1A, alpha-1, and alpha-noradrenergic receptors) (53). Similar mechanisms could also occur after partial lesions and lead to changes in the spinal circuitry. For instance, changes in neuronal properties may occur with chronic exposure to serotoninergic stimulation (2).

The main conclusion of this brief review of multiple types of lesions is that there are several ways through which the CNS and peripheral afferent inputs can access the spinal locomotor circuitry. This apparent redundancy points to the fact that the rhythm is generated at the spinal level and that various degrees of control levels can modulate this spinal circuitry through multiple pathways. The removal of certain pathways produces specific locomotor deficits, but the spinal circuitry and other intact pathways are still able to optimize remnant locomotor functions.

Clinical implications

What are the clinical implications of these concepts? First of all, the evidence is that, in several vertebrates, including mammals such as the cat, the rat, and the mouse, an elaborate circuitry exists in the spinal cord capable of generating the basic locomotor pattern. Some aspects of these basic mechanisms should be conserved in humans and integrated with evolutionary bipedality and greater corticalization. Studies in humans indeed suggest the existence of such a basic spinal circuitry (20, 21, 95, 114, 131). This work shows that involuntary rhythmic activity can be generated at the spinal level in patients with complete or incomplete SCI either spontaneously or through spinal stimulation. According to the preceding strict definition of a CPG, more evidence is required to irrefutably prove the concept of central pattern generation in humans (complete spinalization and neurochemical paralysis). If the basic control design of locomotion in humans is consistent with millions of years of evolutionary biology, then our attitude toward management of humans with SCI should somehow reflect this understanding.

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Locomotor control mechanisms at various levels of the CNS are plastic, as shown by lesions studies, and they are probably amenable to some degree of modifications that could be induced by appropriate interventions. Ongoing clinical trials in humans, using anti-NOGO and anti-Rho, offer tremendous potential to facilitate fiber regrowth. Newly formed or regenerated pathways can, in turn, reach the spinal cord and reestablish contact through short or long propriospinal pathways. Moreover, specific training, such as treadmill locomotor training, maintains optimal function within local spinal circuits capable of generating locomotion and should be viewed as a prerequisite for new connections to function appropriately. Work in various laboratories have indicated beneficial effects of locomotor training in humans or of locomotor activity in general (4, 13, 36, 38, 45), either through the dedication of therapists, through the use of robotic devices, or by spontaneous self locomotor training. In that context, pharmacological stimulation (6) could be helpful, at least initially, in activating and maintaining remnant spinal locomotor functions. These methods, by removing some initial balance and weight support constraints, may altogether improve and maintain spinal locomotor functions so that any new contacts by reorganized descending pathways may find an optimally functioning spinal cord. It should also be expected, as has been clearly shown (66), that new strategies can be added to compensate for specific deficits, which reflect specific spinal lesions, and that locomotor recovery, after incomplete SCI, may result from activating the basic spinal circuitry together with more specific compensatory mechanisms. ■

S. Rossignol holds a Canada Research Chair on the Spinal Cord and is director of the Multidisciplinary Team on Locomotor Rehabilitation after SCI (Strategic Initiative Canadian Institute for Healh Research). He holds funds from the CIHR and The Christopher and Dana Reeve Foundation (CDRF) and is currently on sabbatical at La Pitié-Salpétrière in Paris and funded by the Institut de

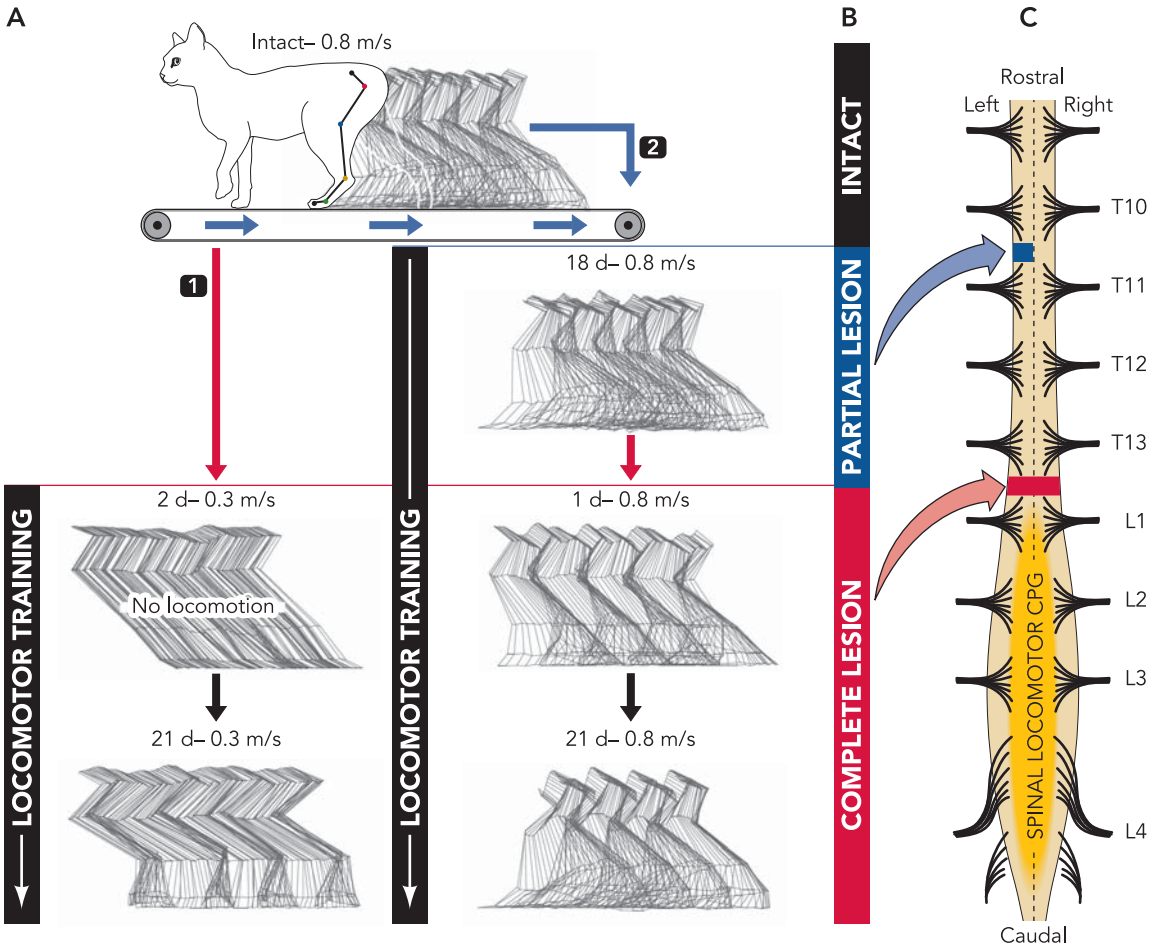

FIGURE 5. **General description of the dual lesion paradigm**
A: locomotion of the left hindlimb is displayed using stick figures reconstructed from light reflecting dots placed on the limb as shown at *top*. The figure illustrates two experimental streams. In *stream 1*, a cat was spinalized at T13 and was paralyzed (2 days). The hindlimbs only dragged on the belt without locomotor movements. After a period of locomotor training (see vertical bar at *left*), the cat walked bilaterally, as shown at 21 days. In *stream 2*, another cat was partially lesioned at T10–T11 on the left side, trained daily (see vertical bar at *left*) and could walk voluntarily on the treadmill with all four limbs (18 days). One day after the complete spinal section at T13, the animal could walk immediately, and further training still improved the gait up to 21 days. *B*: the three conditions of cats as intact, after a partial spinal lesion, and after the complete spinal lesion. *C*: drawing of a spinal cord, indicating the level of the partial lesions (T10–T11) and the complete spinal section (T13–L1), as well as the localization of the spinal locomotor CPG.

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