



Review

## Sensorimotor behaviour following incomplete cervical spinal cord injury in the rat

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### Abstract

Rats are one of the most commonly used species for spinal cord injury research. Since the advent of the Basso, Beattie, Bresnahan (BBB) locomotor rating scale, the majority of spinal cord injury research relies upon evaluating locomotor behaviour in thoracic spinal cord injury rat models. Slightly more than 50% of all traumatic spinal cord injuries in humans, however, occur at the level of the cervical spinal cord. Further, therapies aimed at thoracic spinal cord injuries may not be directly transferable to cervical spinal cord injuries. This could be due to (1) differences in distance between the cell bodies of injured axons and the injury site and (2) because some behaviours (e.g. stepping movements) used to evaluate the therapeutic potential of a given treatment are governed primarily by intraspinal neuronal circuitry while other behaviours (e.g. skilled reaching) require more sophisticated conscious integration of the sensorimotor system. Consequently, there is a need to develop and use experimental cervical spinal cord injury models and understand the behavioural characteristics of such models. The present review highlights the sensorimotor abilities of cervical spinal cord-injured rats, including both forelimb, hind limb, and whole body behaviours. We also provide insight into the neuroanatomic substrates important for performing a given behaviour, information which may prove essential in the development of site-directed therapeutic strategies.

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**Keywords:** Locomotion; Reaching; Spinal cord injury

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## 1. Introduction

Much of what we know about the supraspinal, spinal, and peripheral afferent control of stepping, using quadrupedal mammals, has been gained from using various mammalian animal preparations including decerebrate, immobilized, deafferented, neonatal spinal, and spinalized animal preparations [6,35,79]. Significant contributions regarding the central organization of stepping pattern generation and the development of locomotor systems have also come from research using non-mammalian animals including lamprey, various amphibians, and birds (for reviews, see [17,34,36,37,45,47,68,87]). Of the studies using conscious quadrupedal animals with spinal cord injury (complete or incomplete), the majority of work has been done using thoracic spinal cord-injured rodents (for example, see [14,58,57,63,93,101,107]) and cats (reviewed extensively in [6,27,41,52,80,83,86]). Considering that slightly more than half of the people with spinal cord injury have injuries involving the cervical spinal cord [26,73], and that sensorimotor impairment in these people involves the loss of not only relatively stereotyped movements (e.g. stepping) but also highly integrated sensorimotor behaviours (e.g. skilled forelimb movements), more research needs to be conducted using cervical spinal cord injury (SCI) models. Importantly a majority of quadriplegic patients have identified regaining arm and hand function, not simply locomotor ability or trunk stability, as being a priority in improving their quality of life [1]. Further, because cervical spinal cord injury damages descending axons closer to their neuronal cell body, compared to thoracic spinal cord injury, it is possible that the regenerative potential of descending cervical spinal cord injured axons is greater than that for thoracic spinal cord injuries [29,82].

Since the time of Sherrington [94] and Graham Brown [33], who used predominantly dogs and cats for their work, many researchers have used a variety of mammalian species for conducting experimental SCI including cats, dogs, opossums, mice, rats, guinea pigs, and non-human primates [18,19,35,62,95,98,100,102,103]. With the ever increasing public awareness of animal welfare, and because of increased costs associated with conducting spinal cord research using cats, dogs and primates, many researchers choose to use smaller mammals such as rats. Considering the widespread use of rats for evaluating therapies for experimental SCI, it is important that one understands the behavioural consequence of injuring particular spinal cord pathways in this species.

The present paper reviews what is known about the sensorimotor behavioural consequences of experimentally-induced cervical SCI in adult rats. Understanding similarities and differences of sensorimotor behaviour following cervical SCI compared with the same behaviours following thoracic SCI, will help (1) SCI researchers to identify behaviours that can be exploited to determine the effect of a particular therapy for spinal cord injury using rats and (2) understand the importance of particular neuroanatomic structures in the control of limb movements. The behaviours reviewed herein include skilled forelimb movements, tactile discrimination, general forelimb usage, and flatground and skilled locomotion.

## 2. Forelimb function

Rats are an interesting quadruped in that they use their forelimbs extensively for many tasks [9,8,31,38,39,64,65,119,111,122,112]. This is, in part, why rats are such a useful species for cervical SCI research. Rats use their forelimbs for reaching and grasping, actively sensing their environment, supporting their body weight while rearing, and of course locomotion. Injury to the cervical spinal cord in rats, like all quadrupedal mammals, results in varying degrees of sensorimotor impairments to forelimbs and hind limbs. This section highlights the behavioural consequences of cervical SCI on forelimb function.

### 2.1. Skilled reaching and forelimb somatosensory abilities

Skilled reaching is a sensorimotor ability shared by many species of animals including humans [39]. Skilled reaching requires the integration of both sensory information and motor output. A variety of neural substrates have been identified, in rats, as being important for skilled reaching and these include the cerebral cortex [120,118,115], the corticospinal tract [44,55,110,117,114], red nucleus [121,114], and the basal ganglia [67,116]. Several studies have examined the effects of cervical SCI on skilled reaching abilities of rats [7,24,25,44,55,61,74,91,92,110]. Herein, we review the sensorimotor behavioural effects of bilateral and unilateral cervical spinal cord injury on skilled forelimb reaching.

#### 2.1.1. Bilateral contusive cervical spinal cord injury and skilled reaching

Some of the earliest studies evaluating the effects of injury to the cervical spinal cord on forelimb function in rats comes from work done in the early 1990s [91,92]. Schrimsher and Reier evaluated forelimb motor performance following (1) bilateral dorsal contusion injury and (2) transection injuries to the dorsal columns, dorsolateral funiculi, and ventrolateral funiculi using adult Sprague–Dawley rats. Quantitative and qualitative aspects of skilled reaching for a food pellet were assessed. Bilateral contusive spinal cord injuries were made at cervical spinal segments 4 and 5 (C4–5). Immediately after injury, these animals had complete forelimb and hind limb impairments. By 1 week after spinal cord contusion, the animals were able to maintain a quadrupedal stance. Animals with only a small peripheral rim of white matter sparing (23% white matter sparing) did not regain forelimb reaching capabilities over the 16 week study period [91]. Those animals that regained reaching capabilities had a mean peripheral white matter sparing of 43%. Even in these animals, the percent successful pellet retrieval in animals was impaired for the 16 week duration of the study [91]. It is tempting to conclude that percent white matter sparing is an important constituent for forelimb recovery. Probably more significant determinants are the specific pathways that are spared following injury, rather than the total amount of white matter sparing. For example, sparing of both the ipsilateral dorsal and ventral funiculi, was correlated with improved performance in reaching [91]. Also noteworthy was the finding that animals that regained reaching ability with their forelimb had nearly completely destroyed main

corticospinal tracts with preservation of the fasciculus cuneatus and gracilis. At first glance, it might appear as though the corticospinal tract is not important for skilled reaching. However, it has recently been shown that sparing as little as 1% of the corticospinal system in rats with unilateral destruction of the main dorsal corticospinal tract can result in improved reaching ability of the limb ipsilateral to the spinal cord injury [44]. In addition, because animals with sparing of the ascending components of the dorsal columns were able to regain reaching ability, this implies that sensory information traveling within the dorsal columns are important for reaching. Of those animals that regained the ability to retrieve food, the most common impairments observed were an inability to elevate the limb and reduced shoulder flexion. These impairments were also observed when these animals were removing stickers from their foreheads [91].

Of course, the quantity and quality of reaching ability may be related to the neuroanatomic level of the injury. Injury to the motor neurons at the level of C4–5 would potentially affect forelimb function because these segments contain the motor neurons for the spinodeltoideus, biceps, extensor pollicis longus, and the extensor carpi radialis muscles [60]. Impairment of these muscles would presumably result in an inability to flex the shoulder and elbow, and prevent extension of the carpus.

#### *2.1.2. Specific bilateral spinal cord injuries and skilled forelimb reaching*

One disadvantage to inducing relatively non-specific bilateral damage to the spinal cord is that it is impossible to determine the role or importance of particular spinal pathways in performing a particular task. Consequently, it is important to specifically localize injury to a particular pathway or region of the spinal cord to determine the importance of specific pathways that contribute to a particular behaviour. This is particularly important if one is to produce specific therapies aimed at regenerating or rescuing particular neuroanatomic targets following SCI. Consequently, Schrimsher and Reier attempted to determine the neuroanatomic substrates important for forelimb function by performing selective myelotomies at C4 using Sprague–Dawley rats [92]. This study evaluated the reaching performance of rats following predominantly bilateral lesions to either the dorsal columns (DC), dorsolateral funiculi (DLF) or ventrolateral funiculi (VLF). DC and VLF injured animals did not demonstrate any quantitative differences in pellet retrieval after 2–4 weeks following SCI. Meanwhile, animals with DLF injury had impaired quantitative reaching success up to 4 weeks after injury. Animals with bilateral dorsal column injuries demonstrated impaired lateral spreading of their digits when reaching for a food pellet and held food pellets by squeezing the pellet between the tips of the digits and carpus. In contrast to animals with dorsal spinal injuries, VLF spinal cord injured animals had impairments in shoulder flexion and elbow extension. It was assumed that injury to the vestibulospinal and/or the reticulospinal pathways were responsible for the behavioural changes [92]. The importance of the vestibulospinal system on forelimb reaching needs to be investigated in rats by (1) measuring electrical activity from the major descending vestibular

nuclei during reaching and/or (2) evaluating forelimb reaching following ablation of the main descending vestibular nuclei.

Following cervical DLF injury, rats were unable to grasp food pellets because of an inability to flex their digits [92]. This inability to flex the digits was ascribed to damage to the rubrospinal tract, although studies using red nucleus ablation do not support this finding [114,113]. Animals with unilateral red nucleus lesions are as successful as uninjured animal at grasping food pellets and are also able to flex the digits of the impaired forelimb [114,113]. It is possible that red nucleus lesion studies are not useful for mimicking rubrospinal tract damage. One hypothesis has been put forward that suggests that injury to the rubrospinal tract would be compensated for by the corticospinal tract via a “switching”, or compensation, of lost function between the pyramidal and rubrospinal systems via the rubro-olivary pathway [43]. It is thought that an intact red nucleus (and rubro-olivary pathway) is required for “switching” function from the rubrospinal to the pyramidal system [43]. If one accepts this theory, however, it would be expected that animals with red nucleus lesions would have poorer performance compared to animals with rubrospinal tract injury alone. It is possible that because a specific rubrospinal tract injury is impossible, damage of other spinal tracts (e.g. spinocerebellar pathways) in combination with damage to the rubrospinal tract could account for the discrepancies between the two aforementioned studies. In the future, it would be useful to design a method where rubrospinal axons could be preferentially damaged and then evaluate forelimb reaching movements using high-speed videography and detailed kinematic analysis.

#### *2.1.3. Unilateral cervical spinal cord injury and skilled forelimb reaching*

Recently, skilled forelimb reaching has been examined in rats with unilateral spinal cord hemisections at C5. Unilateral cervical spinal cord hemisected rats (C5) make fewer attempts to reach for a pellet of food and are less successful at retrieving the food pellets when compared to sham-operated animals [3]. Closer examination revealed that rats with C5 cervical spinal cord hemisection were less likely to successfully retrieve a food pellet because of impaired grasping abilities and impaired pronation and supination of the forelimb [3]. However, if an animal had incomplete hemisection, 20% of the reaches made by the animal were considered to have ordinary grasping, supinating, and retracting components [3]. Unilateral damage to the ascending (dorsal column-medial lemniscal and post-synaptic dorsal column pathways) or the descending component (main crossed corticospinal tract) of the cervical spinal cord dorsal column has revealed the importance of these pathways for skilled reaching.

The dorsal column of the rat is made, in part, of ascending fibers of the dorsal column-medial lemniscus and post-synaptic dorsal column pathways. The dorsal column-medial lemniscal pathway is thought to be important for relaying information pertaining to discriminative touch, kinesthesia, pallesthesia, graphesthesia, certain aspects of stereognosis, and proprioception (for review, see [23]). Meanwhile, the post-synaptic dorsal column pathway is important for signaling visceral pain [123], mechanosensation [4], and both mechano- and

thermal nociception [4]. Recently, the ascending components of the dorsal columns were investigated with respect to their importance in performing skilled reaching in the rat [61]. Unilateral dorsal column (DC) injury, produced by unilaterally incising the ascending component of the dorsal column at C2, was performed to assess the importance of this pathway on goal-directed skilled reaching [61]. Because this study created an injury at C2, none of the motor neurons for the forelimb musculature were affected [60]. Interestingly, animals with these injuries initially had poor success at retrieving food pellets. These quantitative deficits disappeared by 7 days following SCI. Careful semi-quantitative kinematic analysis (based on Eshkol–Wachman movement notation) revealed that DC-injured rats recovered food retrieval ability by making adjustments in whole body and forelimb movements when retrieving a single food pellet [61]. These kinematic findings do not support those previously reported for one rat with unilateral dorsal column injury performing a similar task [92]. This discrepancy can most likely be explained by a difference in data analysis [61]. Regardless, specific impairments of the forelimb ipsilateral to the DC injury included: (1) an inability to adduct the elbow, (2) lack of pronation of the paw during grasping the pellet, and (3) abnormal supination of the paw while withdrawing the food pellet from the food tray to the animal's mouth [61]. Aside from identifying the ascending components of the dorsal columns as being important for skilled reaching, this study illustrates that although an endpoint may be achieved, the way in which the animal behaves while reaching a particular endpoint can be significantly altered compared with behaviours observed before surgical and/or therapeutic intervention.

The corticospinal tract (CST), descends ipsilaterally via the ventral funiculus, but predominantly (~95%) descends contralaterally from the sensorimotor cortex within the dorsal columns in the rat [20,110]. The CST extends throughout the length of the spinal cord in rats [20,22,99]. The CST projects to the dorsal horn and the intermediate gray matter (laminae V–VII) with only some terminations on long propriospinal neurons within lamina VIII or motor neurons in the ventral horn [5,21,22]. The corticospinal system is of particular interest in human medicine because of its importance in motor control [53,72,71]. Recent studies evaluating the behavioural effects of corticospinal tract injuries, within the cervical spinal cord, have identified this tract's importance for skilled forelimb behaviour in the rat [44,55,110]. Following unilateral electrolytic injury to the main dorsal corticospinal tract, ambidextrous rats are less successful at retrieving a piece of food with the forelimb ipsilateral to the spinal cord injury [44,55]. Reaching success is proportional to CST sparing. It has furthermore been demonstrated that as little as 1% sparing of the main dorsal CST can result in some improvement in reaching success [44]. It has been previously shown that rats are able to recover quantitative reaching abilities following injury to the ascending components of the dorsal column [61]. Consequently, it seems likely that impaired reaching success following dorsal CST tract injury is due to the CST injury and not the small amount of damage to the ascending pathways of the dorsal column that were created during electrolysis of the CST. Evidence regarding the neuroanatomic plasticity that

accounts for spontaneous improvement in behavioural recovery following bilateral cervical CST injury in the rat is beginning to accumulate [110]. Specifically, spontaneous recovery of forelimb reaching attained following bilateral dorsal column CST injury, at C2 spinal cord segment, is prevented when the ventral CST is injured together with the dorsal CST [110]. When the dorsal CST is injured alone, it was shown that the ventral CST began sprouting onto medially located motor neurons in the ventral gray matter [110]. This sprouting coincided with spontaneous forelimb recovery at 4 weeks post-spinal cord injury [110]. In addition, spontaneous forelimb recovery following bilateral dorsal CST injury is abolished following subsequent injury of the ventral CST [110]. Therefore, it appears as though the sprouting and reorganization of synaptic contacts of the CST onto the motor neurons in the ventral gray matter is responsible, in part, for the improved behavioural recovery following bilateral dorsal CST injury in the rat [110]. Evidence regarding spontaneous sprouting of the cervical CST onto long propriospinal axons following CST injury, within the thoracic spinal cord, has been described [11]. This sprouting too was shown to be responsible for the behavioural recovery of the hind limbs of these spinal cord-injured rats [11]. The importance of such neuroanatomic plasticity likely accounts for much of the behavioural plasticity seen in animals, including humans, following spinal cord injury. Such changes need to be taken into account when evaluating the efficacy of particular therapies. Researchers must be able to identify and delineate the behavioural recovery that occurs spontaneously versus that which may be attributable to the given therapy when using incomplete spinal cord injury models. As such, a battery of appropriate behavioural tests for forelimb function should be employed as has been suggested for the evaluation of animals following thoracic spinal cord injury [32,51,63,70,106].

## 2.2. Other forelimb behaviours

Rats are able to perform a variety of unskilled forelimb movements that serve a variety of purposes. Three such behaviours include the placing reaction, paw usage during vertically-oriented exploratory behaviour, and forelimb grip strength. These behaviours are naturally occurring and do not require specific training of the animal in order to be examined and evaluated.

The placing reaction can be evoked by visual or tactile stimuli. Tactile stimulus-induced placing can be induced by contacting either the nasal vibrissae or dorsum of the forepaw to a horizontally placed surface. Contact of the nasal vibrissae or the dorsum of the forepaw causes a rat to flex its forelimb and place its paw onto the surface. The exact neural pathways important for eliciting pedal-induced contact placing are unknown (see [107] for brief review). Both tactile and vibrissae stimulus-induced placing have been examined following cervical SCI in rats. Rats with bilateral contusion injury to C4–5 have an impaired ability to flex their shoulders during vibrissae-induced placing [91]. Further it has been shown that rats with bilateral contusion injury at C5 are less successful at performing vibrissae-stimulated placing responses with increasing severity of spinal cord injury [78]. For example, average percentage of “successful” paw placements for rats with no spinal cord injury

or mild, moderate, and severe bilateral contusion injury at C5 has been reported to be 88%, 85%, 42%, and 1.5%, respectively [78]. Animals with unilateral injury to the cervical spinal cord (at C3 or C4) have distinct reductions in pedal or vibrissae-induced placing responses with the forelimb ipsilateral to the SCI [90,107]. A more thorough analysis, using high speed videography and/or electromyography, is required to decipher the exact impairments of forelimb placing following cervical SCI.

Rats use their forelimbs for balance and support during rearing against a vertical surface. Recently, a detailed behavioural analysis has described the vertical and horizontal movements of rats behaving during the “cylinder test” [31]. This test has been used following unilateral cervical spinal cord transection, contusion, and aspiration [7,56,78,90,97,104,108,109]. It is, however, important to recognize that the utility and/or interpretation of the “cylinder test” will be affected by impaired hind limb function in cervical spinal cord-injured animals. It has been shown that uninjured, freely behaving rats use each limb separately approximately 25% of the time and use both limbs together simultaneously the remaining 50% of the time [56,90,97,105]. Limb preference for vertical support while rearing is conserved between strains of rats [105]. It has recently been demonstrated that rats with moderate, but not mild, bilateral contusion injury to the cervical spinal cord use both paws together more often than using a single forelimb for body weight support when rearing against a vertical surface compared to uninjured animals [78]. It should be noted that rats with extensive damage to the gray and white matter at C5 will not and/or cannot rear against a vertical surface [78]. Nevertheless, we and others have demonstrated that the rubrospinal tract appears to be important for producing this behaviour. When the cervical rubrospinal tract is injured unilaterally, rats use the limb ipsilateral to the injury significantly less than the contralateral limb [56,108]. It is, however, unclear whether the ascending components of the dorsal columns are important for performing this behaviour. Two recent studies examining the effects of unilateral injury to the cervical dorsal column (excluding the main corticospinal tract) have found conflicting results regarding limb usage while rearing [7,108]. These discrepancies may be, in part, due to differences in the extent of the injury. Another recent study examined the effects of unilateral injury to the C3 ventrolateral funiculus on forelimb function while rearing [109]. This study demonstrated that injury to the ventrolateral funiculus of the C3 spinal segment did not result in permanent disuse of the forelimb ipsilateral to the spinal injury [109]. As already alluded to, it does not appear as though pathways running in the ventrolateral quadrant of C3 are important for forelimb use while rearing. When these pathways are injured unilaterally, animals regain the ability to use the forelimb ipsilateral to the injury by 2.5 weeks following SCI [109]. The regained function is most likely a result of neuroanatomic plasticity; that is, remaining intact pathways may sprout and/or become active following spinal cord injury similar to that described for the corticospinal system [110].

Mice, and rats, will naturally reach and grasp an object when they are suspended in the air and the object is brought in front of their forepaws [3,66,76,78]. This naturally occurring behaviour has been exploited to evaluate an animal's grip

strength [2,3,28,59,66]. Alterations and recovery in grip strength have been recently investigated in mice and rats with cervical spinal cord injury [2,3,76,78]. Grip strength testing has been shown to provide reliable, quantitative data that can be used to assess recovery of forelimb function following cervical spinal cord injury [2,3,78]. Bilateral contusion injury at C5 in rats results in reduced grip strength and a reduced ability to support body weight while grasping an elevated horizontal rod [78]. As would be predicted, grip strength is reduced with increasing severity of spinal cord injury [78]. In mice with lateral cervical spinal cord hemisection (at C5 or C6 or C7 or T1), grip strength of the forelimb ipsilateral to the spinal cord injury was found to be absent up to 14 days, with relatively minor reductions of grip strength of the contralateral forelimb, following spinal cord injury [2]. Grip strength of the forelimb ipsilateral to the cervical spinal cord hemisection at C5 returns to  $\leq 50\%$  of baseline by 3 weeks following spinal cord injury in mice [2]. Interestingly, complete lateral hemisection at C5 in rats results in absent gripping ability of the ipsilateral forelimb up to 8 weeks following spinal cord injury. Meanwhile, grip strength of the contralateral limb, regardless of the level of the cervical spinal cord injury, completely recovers following cervical spinal cord hemisection in both mice and rats [2,3]. Adult rats with bilateral contusion injury of C7 spinal cord segment, however, only regain approximately 37% of their original forelimb grip strength [76]. Although it is obvious how cervical spinal cord injury affecting the motor neuron pools for the forelimb musculature would affect forelimb grip strength, it has yet to be determined how grip strength would be affected in rats and mice with spinal cord injuries not involving these motor neuron pools.

### 2.3. Cervical spinal cord injury and forelimb somatosensation

Skilled reaching and other forelimb behaviours require the integration of both sensory and motor systems. Considering that unilateral injury to the dorsal columns of the cervical spinal cord results in transiently poor success in reaching for a pellet, and that rats adapt a new means by which to successfully grasp a pellet of food, it implies that somatosensation is an important aspect of forelimb function. Further work has demonstrated that rats with unilateral cervical dorsal column (excluding main corticospinal pathway) injury lack haptic discrimination, that is, they lack the ability to discriminate surfaces of different textures [7]. A very simple, yet clever, experiment was designed such that rats were trained, before cervical SCI, to discriminate between food (pasta) and non-food (drill bit) items based on the item's texture. In addition, the effects of dorsal column injury on kinetic aspects of grasping were determined by comparing pre- and post-surgery grasping force. Following unilateral cervical dorsal column injury, at C2, animals could no longer discriminate between the food and non-food items (Fig. 1). Nevertheless, injured rats were still able to generate the vertical, fore-aft, and medio-lateral forces necessary to break a piece of vertically-oriented pasta (Fig. 2). Future studies need to be designed to examine the importance of other sensory pathways, within the cervical spinal cord, on skilled forelimb reaching.

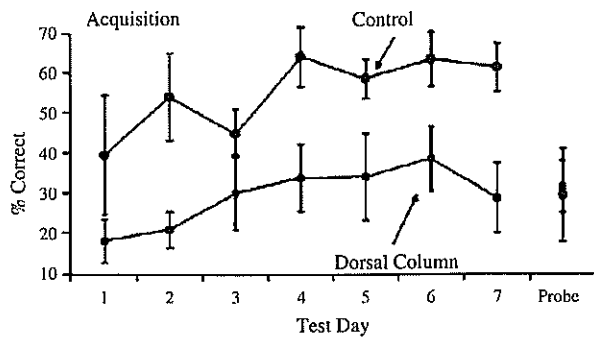


Fig. 1. Percent correct responses for choosing between a food item and non-food item in adult female Long-Evans rats with unilateral transection of the ascending components of the spinal dorsal columns. Transections were located at cervical level 2 on the side ipsilateral to the preferred limb for reaching. Animals were tested beginning on day 20 following surgery (day 1). Note that dorsal column injured animals were less likely to discriminate between the pasta (food item) and a serrated drill bit (non-food item) compared to control. During a probe trial, both control and dorsal column injured animals could not learn to discriminate between a smooth non-food item and an equivalently sized piece of smooth pasta. Dorsal column, injured animals; control, non-injured animals. (Reprinted with permission from Ballermann, McKenna and Whishaw, Brain Res. Bull., 2001.)

For example, training rats to discriminate between food items based on thermal sensation might be useful for determining the importance of ventrolateral pathways for conducting sensations of thermally-induced pain. Moreover, such studies might produce useful models for studying recovery of particular sensory modalities following experimental therapies for SCI in rats.

In another study, forelimb somatosensory loss following bilateral cervical spinal cord injury was investigated [77]. Specifically, the time to notice a sticker on the palm of the forepaw was assessed in rats following bilateral dorsal or dorsolateral funiculotomy, or dorsal hemisection at spinal cord segment C4 [77]. It was shown that destruction of the ascending portions of the dorsal columns, but not the dorsolateral funiculus, results in a loss of somatosensory-evoked potentials evoked by electrical stimulation of the forepaw [77]. In addition the time taken for an animal to notice the sticker on the palm of the forepaw was prolonged 1 week following dorsal column injury [77]. These findings support the hypothesis that sensory pathways in the dorsal column but not the dorsolateral funiculi are important for cutaneous sensation. Interestingly, it was found that if animals with dorsal hemisection of their C4 spinal cord segment were tested weekly, for 4 weeks following spinal cord injury, the time taken to first notice the sticker became shorter over the 4 week time period [77]. Further investigation demonstrated this "improved" sensory function was a result of "learning" or "training" [77]. Specifically, dorsal spinal cord-hemisectioned animals, tested only at 4 weeks following spinal cord injury, did not demonstrate reduced time taken to notice the adhesive sticker on the palm of their paw. Potential anatomical or physiological phenomenon accounting for this behavioural recovery were not determined [77]. It is, however, important to recognize that improvement in behavioural recovery can occur with "training" or repeated performance of a task (for review, see [69,81,124]). The phenomenon of behavioural plasticity should

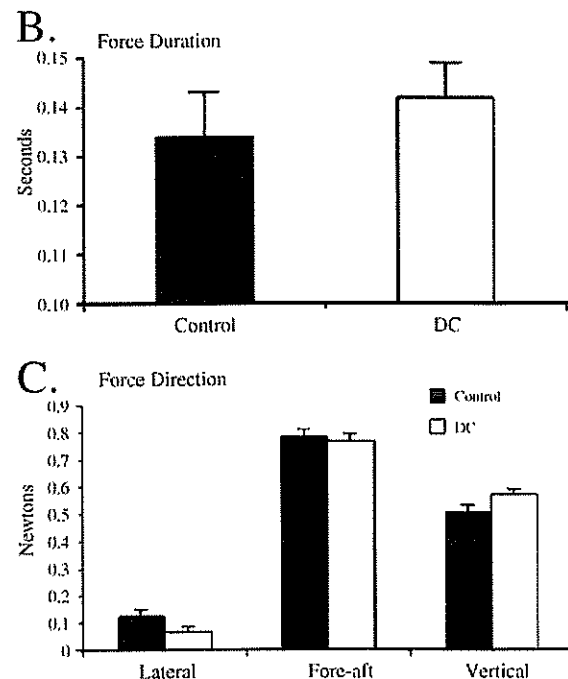
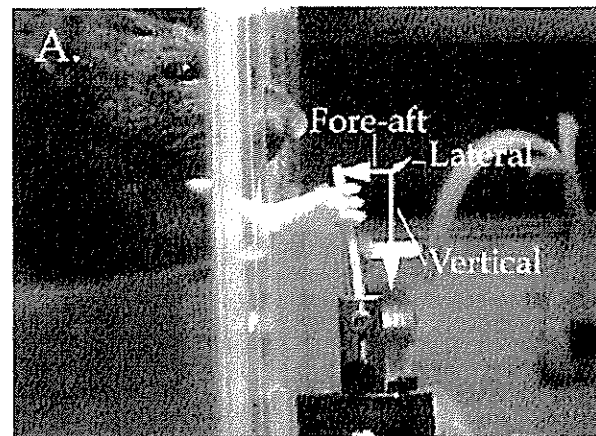


Fig. 2. Forces exerted by the forelimbs while obtaining a pasta food reward in rats with (DC) and without (Control) unilateral cervical dorsal column transection. Note that dorsal column injured rats exert forces of similar duration (B) and magnitude (C) in the fore-aft, lateral, and vertical forces when breaking a piece of pasta (A). Consequently, the ascending components of the dorsal columns do not appear to impair force production while reaching. (Reprinted with permission from Ballermann, McKenna and Whishaw, Brain Res. Bull., 2001.)

be taken into account when comparing results obtained from different laboratories or when different protocols for behavioural assessment are used within the same laboratory.

### 3. Locomotion

In order to locomote effectively over a variety of terrains, animals that have legs must be able to produce stepping movements, maintain balance and posture, and be able to maneuver over a variety of different physical obstacles. Locomotion can be measured as: (1) an endpoint—e.g. does the animal successfully move from one point to another, (2) kinematically—describing

how the animal's limb(s) and/or body moves in space or, (3) kinetically—describing the forces that the limb exerts (e.g. on the ground, between joints, etc.). All of these methods have been used to evaluate locomotion in spinal cord-injured rats (for review, see [51,70,106]). A more detailed review of the methods that can be used for evaluating behaviour of spinal cord-injured rats can be found elsewhere (see [70]).

As previously mentioned, few studies have critically evaluated the locomotor abilities of cervical spinal cord-injured rats [77,97,104,107,108], and the vast majority of our knowledge pertaining to the nervous control of adult locomotion and stepping in mammalian quadrupeds comes from work done in cats (for reviews, see [6,35,52,85,88,84]). It is important, however, to note that the identification of the central pattern generators for the fore and hind limbs has been determined for neonatal rats [10,50] and their locations are similar, although not identical, to those of other mammalian species [46]. Specifically, neonatal rat forelimb central pattern generators are located within C7–T1 spinal cord segments [10], while hind limb central pattern generators are located within the low thoracic (T11–13) and throughout the lumbar spinal cord (L1–L6) (for review, see [45]). Studies evaluating recovery of locomotor behaviour following cervical SCI in the rat are necessary; particularly if we are to evaluate the effects of a specific therapy or to design specific therapies for cervical spinal cord-injured animals, including humans.

Until recently, no information existed regarding the spontaneous locomotor abilities of rats with bilateral cervical SCI [78]. In part, this is most likely because of a variety of factors including: (1) the relatively high amount of nursing care that bilaterally cervical spinal cord-injured rats require compared to thoracic spinal cord-injured animals; (2) an increase in the expected mortality of the experimental subjects. For example, in one laboratory, mortality rates ranging from 0–30% have been reported following graded bilateral contusion injury at C5 in rats [78]. As would be expected, mortality rates increase with increasing severity of injury [78]. Meanwhile, these mortality rates are considerably higher than the reported mortality rate of less than 1.2% for thoracic spinal cord-injured rats [78]. Nevertheless, it has been reported, that rats with C4–5 SCI induced using a contusion weight drop method (10 g weight dropped 2.5 cm) are able to maintain a quadrupedal stance as early as 7 days after injury [91]. A more detailed analysis of locomotor abilities of bilateral cervical (C5) SCI rats revealed that forelimb and hindlimb step lengths decrease while forelimb and hind limb base of support (distance between paw prints during locomotion) and the degree of paw exorotation both increase during locomotion as the severity of SCI increases [78].

The development of the Basso, Beattie, Bresnahan (BBB) scoring system [12] has enabled researchers to efficiently and reproducibly evaluate the locomotor abilities of thoracic spinal cord-injured rats [15]. Ordinal rating scales have also been developed for specific use in thoracic spinal cord-injured dogs and mice [16,75]. The BBB locomotor rating scale is a 22 point ordinal rating scale. An animal's locomotor abilities are scored from 0 to 21. Zero denotes an animal with complete paralysis of their hind limbs, while animals with normal locomotor abilities (hind limb joint movement, weight support, interlimb

coordination, etc.) are scored 21 points [12,13]. The scale was developed based upon the natural progression of locomotor recovery in rats with thoracic spinal cord injuries. The BBB locomotor rating scale grossly assesses hind limb movements, body weight support, fore–hind limb coordination, and whole body movements throughout the recovery period. In the later stages of recovery, the BBB scale predominantly discriminates an animal's locomotor abilities by evaluating the movement of the hind limbs [12]. Researchers need to be cognizant of the fact that methods used for evaluating thoracic spinal cord-injured animals may not be appropriate when evaluating cervical spinal cord-injured rats. Recently, conflicting results have been reported with respect to hind limb behaviour in cervical spinal cord-hemisected (CH) rats [96,107]. Specifically, one study found that CH (C3) rats displayed no impairments of motor function of these animals' hind limbs [107] using the BBB scoring system while the other study demonstrated significantly impaired motor abilities of CH (C3–C4) animals' hind limbs [96]. Details of these studies will be discussed below but it appears that the differences in results may be, in part, due to differences in surgical methods and in the spinal level of the lesion, causing different degrees of ipsilateral forelimb impairment.

Rats with CH at C2, C3, C3–C4, or C5 typically display varying degrees of gross forelimb movement while locomoting [3,30,96,107]. At rest, CH (C3) rats may lie in sternal recumbency or stand with a quadrupedal or tripod stance (forelimb ipsilateral to the hemisection is lifted off the ground) [107]. During exploratory locomotion, CH rats will occasionally open the paws ipsilateral to the SCI during stance and balance themselves with the limb contralateral to the SCI when rearing [96,107]. In addition, CH rats preferentially groom themselves with the limb contralateral to the SCI [107]. During treadmill and goal-directed locomotion, CH rats tend to have shorter range of shoulder motion, causing a decrease in stride length [96,107]. Lateral cervical spinal cord-hemisected rats have varying incidences of dorsal stepping (bearing weight on the dorsum of the paw), with the forelimb ipsilateral to the SCI during treadmill or goal-directed unrestrained locomotion [96,107]. These severe forelimb impairments following cervical SCI most likely cause a loss of balance resulting in a compensatory response of the hind limbs, as observed by hind limb exorotation, altered fore–hind, fore–fore, and hind–hind interlimb coordination, truncal ataxia, and impaired weight support. All of these changes in behaviour would presumably affect the final BBB score given to a particular animal. Consequently, there is a need for a scoring system specifically designed for cervical spinal cord-injured rats.

We have recently shown that rats with cervical spinal cord hemisection at C3, have moderate forelimb dysfunction and have gross hind limb locomotor abilities similar to sham operated control animals [107]. More detailed kinetic analysis of the locomotor abilities of these CH rats revealed, however, that these animals in fact used their hind limbs similarly to rats with unilateral hemisection of the thoracic spinal cord. Of course, cervical spinal cord-injured rats had more impaired forelimbs ipsilateral to the SCI compared to thoracic hemisected animals. Interestingly, CH rats behave biomechanically



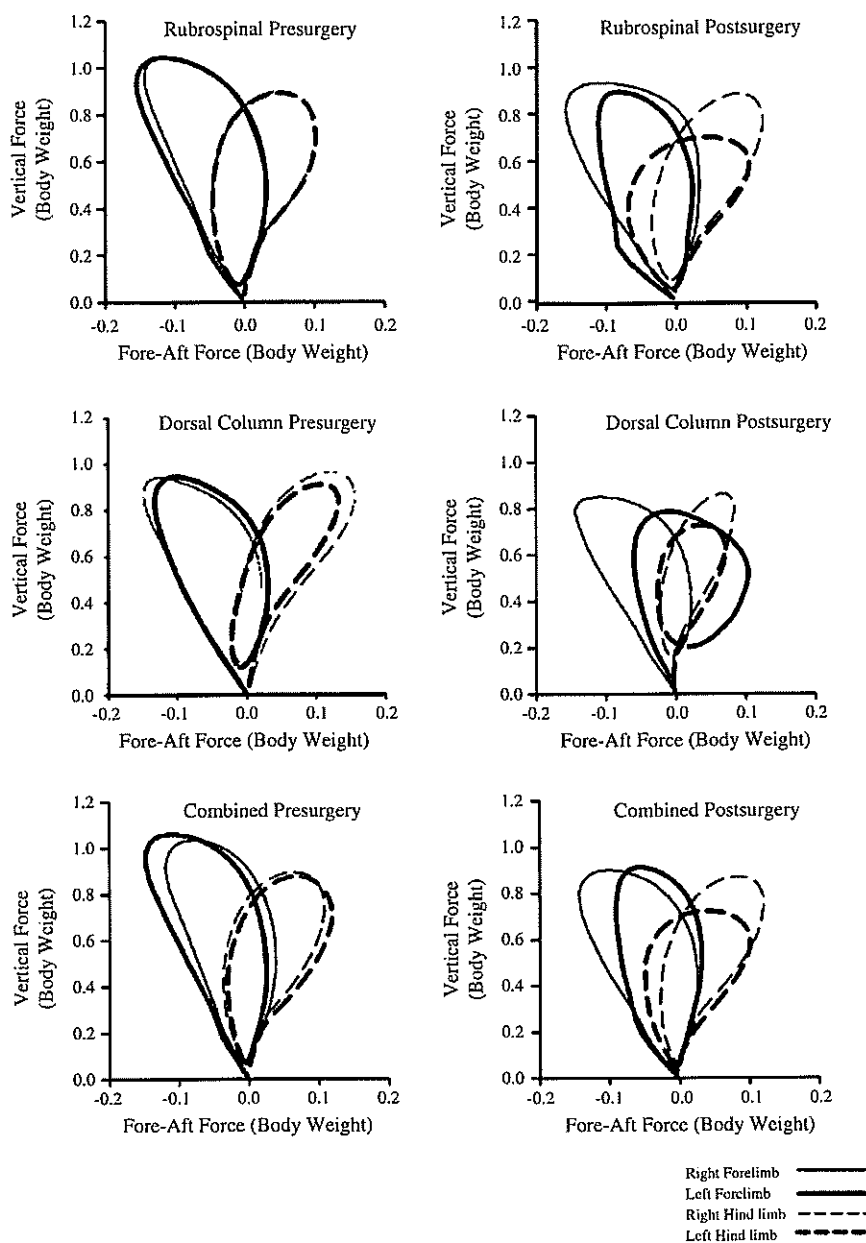


Fig. 3. Vector dynamograms demonstrating limb symmetries for rats before spinal cord injury and 6 weeks following unilateral (left-sided) rubrospinal, ascending dorsal column, or combined rubrospinal/ascending dorsal column injuries made at C3. Note that unilateral spinal cord-injured animals used the hindlimb ipsilateral to the injury significantly less for weight bearing than before surgery. (Reprinted with permission from Webb and Muir, *Eur. J. Neurosci.*, 2003, Blackwell Science.)

similarly to animals with unilateral forelimb amputation [49]. This similarity may be because of the change in the animal's body center of mass. Not surprisingly, both CH rats [107] and dogs with unilateral forelimb amputation [49] typically shift more body weight caudally, thus moving the center of mass more caudally. Furthermore, rats with cervical or thoracic spinal cord hemisection use the forelimb ipsilateral to the SCI less for braking than do sham-operated animals [104,107]. In addition, cervical and thoracic spinal hemisected rats share similarities in interlimb coordination during trotting. For instance, cervical and thoracic SCI rats place the forelimb ipsilateral to the SCI on the ground just after the contralateral hind limb has been placed

on the ground [107]. Uninjured trotting rats alternately place diagonal limb pairs on the ground simultaneously [105,107].

As opposed to the relatively stereotyped movements involved with flatground locomotion, skilled locomotion requires (1) the ability to rapidly adjust muscle length and tension, (2) a high degree of intra- and interlimb coordination, and (3) the ability to voluntarily and rapidly adjust portions of the step cycle. Skilled locomotion (over a rope, wooden dowel, beam, grid or ladder) is affected in a variety of rat models of cervical spinal cord injury including; bilateral and unilateral dorsal contusion, unilateral spinal cord hemisection, dorsal spinal cord-hemisection, and dorsal funiculus demyelination [3,40,48,54,77,89,96,97]. Rats



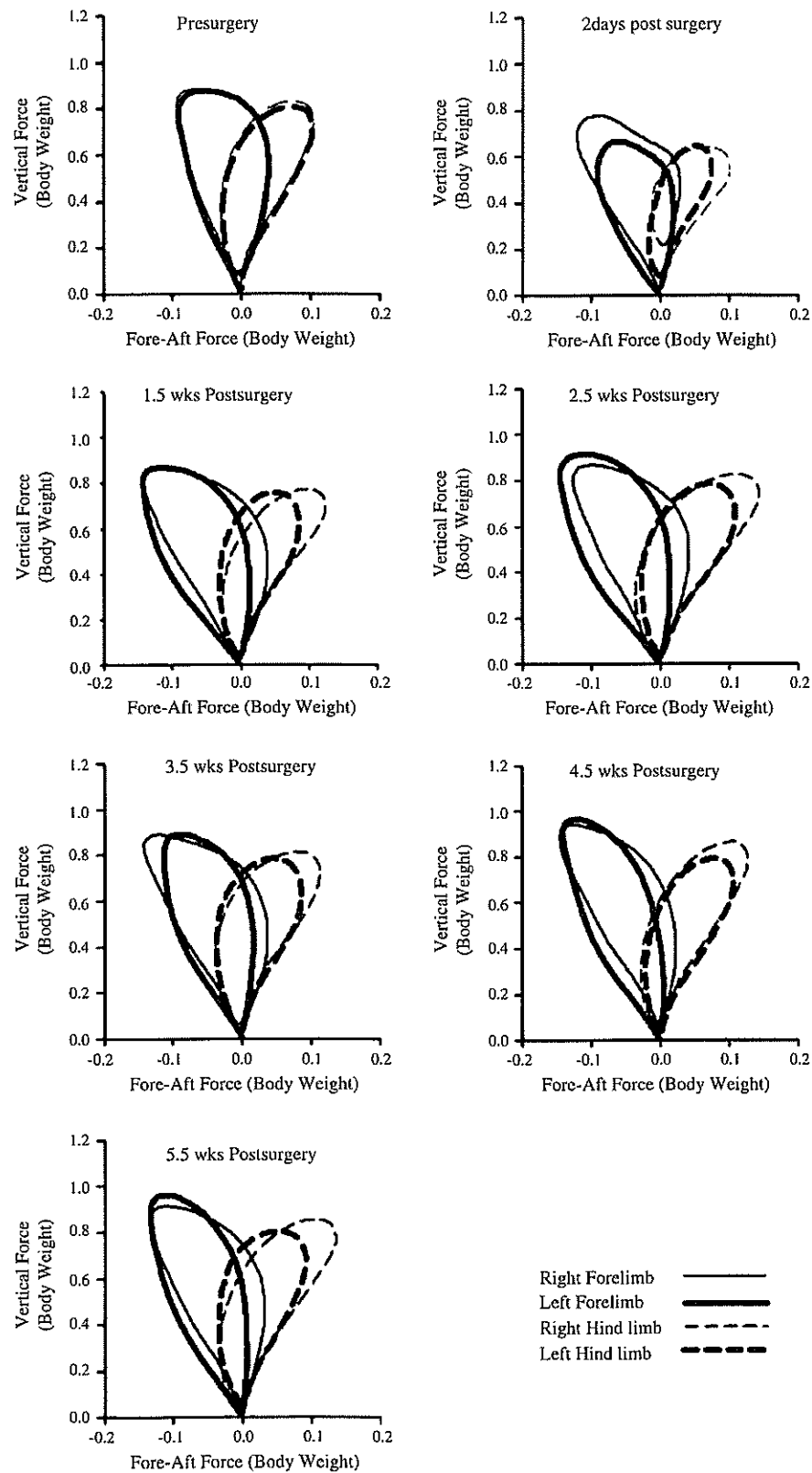


Fig. 4. Vector dynamograms depicting right-left limb symmetries for unilateral (left-sided), ventrolateral (ULVL) spinal funiculus-injured rats before and up to 5.5 weeks following spinal cord injury. Two days following injury ULVL injury less weight on the forelimb ipsilateral to the injury compared to the contralateral forelimb. Interestingly, very mild, yet persistent hind limb asymmetries were observed up to 5.5 weeks following spinal cord injury. Specifically, the hindlimb ipsilateral to the injury bore less weight than the contralateral hindlimb. (Reprinted with permission from Webb and Muir, *Behav. Brain Res.*, 2004.)

with bilateral dorsal contusion injury at C5 made more footfalls while traversing a horizontally placed ladder with irregularly spaced ladder rungs [78]. As might be expected, the number of footfalls made increase with more severe spinal cord injury [78]. Interestingly, however, rats bilateral contusion injury at C5 made similar numbers of footfalls with their forelimbs compared to their hind limbs [78]. Following unilateral cervical spinal cord hemisection or contusion, rats misplace their limbs more frequently when performing skilled locomotion over a ladder [96,97]. These findings are consistent with those found for CH cats [42]. Interestingly, CH rats and cats have more foot placement errors with the limbs ipsilateral to the SCI [42,96] largely due to ipsilateral forelimb errors [96]. Similarly, rats with dorsal or dorsolateral spinal cord injuries make more footslips with their forelimb compared to their hind limbs while locomoting across a grid [77]. It could be that the hind limbs are less affected while locomoting across a ladder or grid, following unilateral cervical SCI, because of the increased likelihood of bilateral or contralateral innervation of hind limb spinal premotor or motor neurons by intact descending spinal pathways.

The locomotor adjustments that CH rats make have been exploited to determine the importance of the rubrospinal tract, ascending components of the dorsal columns, and pathways within the ventrolateral funiculus in locomotion (Fig. 3) [104,108]. We have shown that unilateral injury to the dorsolateral funiculus and ascending components of the dorsal column results in long-lasting changes in both flatground and skilled locomotor abilities of adult freely behaving rats (Fig. 3) [108]. Consequently, the pathways running within the dorsolateral funiculus and the sensory portion of the dorsal column of the cervical spinal cord appear to be important for locomotion [108]. Unilateral injury to the ventrolateral funiculus of the cervical spinal cord, however, results in locomotor alterations that return to normal by 5.5 weeks following SCI (Fig. 4) [104].

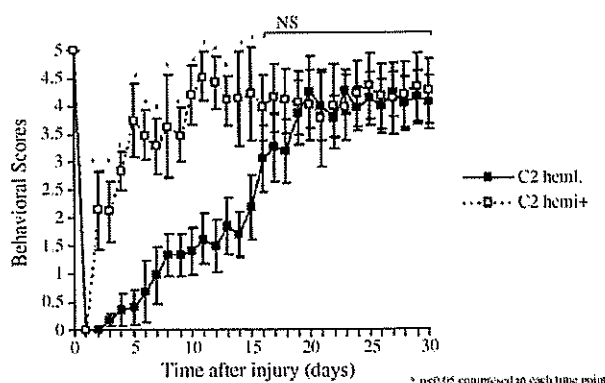


Fig. 5. Behavioural scores representing the degree of left forelimb impairment following left C2 spinal cord hemisection, with (C2 hemi+) or without (C2 hemi-) contralateral dorsal and ventral spinal root transection, in adult female Sprague–Dawley rats. Forelimb behaviour was scored using a modified Tarlov scale (0, complete paralysis to 5, nearly normal walking behaviour). Interestingly, the forelimb rate of improvement was significantly greater in the C2 hemi+ group, indicating that contralateral nerve root transection induced plastic changes within the spinal cord, probably by awakening “silent” synapses similar to that observed in the crossed phrenic phenomenon. (Reprinted with permission from Fujiki et al., *Exp. Neurol.*, 2004.)

This implies that pathways running in the ventrolateral funiculus are not important for locomotion when injured by themselves unilaterally and/or that any functional loss is compensated for by the remaining pathways including those in the ipsilateral ventral funiculus and/or contralateral ventral and ventrolateral funiculi [57]. For example, it has been recently shown that forelimb recovery, during locomotion, can be induced by transecting the contralateral dorsal and ventral spinal roots, a phenomenon similar to that of the crossed phrenic phenomenon (Fig. 5) [30]. This evoked recovery is likely due, in part, to a consequence of plastic changes involving the contralateral reticulospinal tract and its associated neurotransmitter, serotonin. It was shown that the evoked recovery could be prevented by a selective serotonin synthesis inhibitor [30].

#### 4. Relevance and general conclusions

Cervical spinal cord injury results in unique sensorimotor behaviours in rats. These behaviours are beginning to be evaluated in studies evaluating therapies for SCI. The present review identifies specific alterations in sensorimotor behaviours for both the fore and hind limbs following cervical SCI in adult rats. In the instance of partial cervical SCI, the forelimbs appear to be affected more profoundly than the hind limbs. However, immediately after cervical SCI, fore and hind limbs may be affected equally. These findings suggest that considerable neuroanatomic and/or neurochemical changes may occur in the premotor or motor neuron networks of the hind limbs. In some instances, however, permanent behavioural changes for both fore and hind limbs suggest that particular anatomic pathways are more important than others for performing a particular behaviour. The identification of the neuroanatomic substrates responsible for particular behaviours will become essential for focusing experimental therapies, such as intraspinal microstimulation, transplantation and neural regenerative strategies, toward particular spinal pathways.

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