Acta Physiol 2007, **189,** 155–169

REVIEW

Spinal cord plasticity in acquisition and maintenance of motor skills

J. R. Wolpaw

Wadsworth Center, Laboratory of Nervous System Disorders, New York State Department of Health and State University of New York, Albany, NY, USA

Received 14 June 2006, accepted 21 August 2006
Correspondence: J. R. Wolpaw MD, Wadsworth Center, New York State Department of Health and State University of New York, PO Box 509, Empire State Plaza, Albany, NY 12201-0509, USA.
E-mail: wolpaw@wadsworth.org

Abstract

Throughout normal life, activity-dependent plasticity occurs in the spinal cord as well as in brain. Like other central nervous system (CNS) plasticity, spinal cord plasticity can occur at numerous neuronal and synaptic sites and through a variety of mechanisms. Spinal cord plasticity is prominent early in life and contributes to mastery of standard behaviours like locomotion and rapid withdrawal from pain. Later in life, spinal cord plasticity has a role in acquisition and maintenance of new motor skills, and in compensation for peripheral and central changes accompanying ageing, disease and trauma. Mastery of the simplest behaviours is accompanied by complex spinal and supraspinal plasticity. This complexity is necessary, in order to preserve the complete behavioural repertoire, and is also inevitable, due to the ubiquity of activity-dependent CNS plasticity. Explorations of spinal cord plasticity are necessary for understanding motor skills. Furthermore, the spinal cord's comparative simplicity and accessibility makes it a logical starting point for studying skill acquisition. Induction and guidance of activity-dependent spinal cord plasticity will probably play an important role in realization of effective new rehabilitation methods for spinal cord injuries, cerebral palsy and other motor disorders.

Keywords conditioning, H-reflex, learning, memory, motor function, plasticity, rehabilitation, spinal cord injury.

Motor skills can be described as 'adaptive behaviours acquired through practice' (Compact OED 1993). Traditional concepts of the nervous system plasticity responsible for these skills have assumed that this plasticity occurs in only a few very specific locations and by only a limited number of mechanisms, and have focused most attention on the cortex, cerebellum and closely related brain regions. However, much recent evidence indicates that this traditional view is not correct. It is now abundantly clear that activity-dependent plasticity is ubiquitous in the central nervous system (CNS). New appreciation of the many kinds of synaptic and neuronal plasticity, of their presence in many different areas, and of the frequency with which they occur, has overturned the traditional view of a hardwired CNS that acquires skills through only a few mechanisms at only a few specialized sites. Activity-dependent plasticity is now recognized as a feature of the entire CNS.

In response to this new understanding, research aimed at understanding the plasticity underlying new behaviours now focuses strongly on simple models for which the neuronal circuitry undergoing activity-dependent plasticity is defined and accessible. Both invertebrate and vertebrate models have been developed. Prominent examples include Aplysia siphon withdrawal, vestibulo-ocular reflex (VOR) adaptation, eye-blink conditioning and fear conditioning (Cohen *et al.* 1997, Lieb & Frost 1997, Thompson *et al.* 1997, Lisberger 1998, Garcia *et al.* 1999, Hansel *et al.* 2001,

 doi: 10.1111/j.1748-1716.2006.01656.x

King *et al.* 2001, van Alphen & De Zeeuw 2002, Medina *et al.* 2002, Vaynman & Gomez-Pinilla 2005). For this research endeavour, it would seem that the spinal cord has distinct advantages, for its neuronal circuitry is relatively simple and accessible and supports a variety of simple behaviours. Like plasticity elsewhere in the CNS, spinal cord plasticity involves both synaptic and neuronal mechanisms [e.g. long-term potentiation (LTP), modifications in neuronal morphology and electrical properties], is affected by growth factors, and is associated with gene activation (e.g. Liu & Sandkühler 1997, Eyre *et al.* 2000, Gibson *et al.* 2000, Inglis *et al.* 2000, Mendell *et al.* 2001, Wolpaw & Tennissen 2001, Tillakaratne *et al.* 2002, Dupont-Versteegden *et al.* 2004, Ding *et al.* 2005). Furthermore, unlike the circuitry underlying the VOR, the conditioned eye blink, and other vertebrate models, spinal cord circuitry is easily separable from the rest of the CNS, so that plasticity occurring within it in the course of skill acquisition can be studied in isolation. However, in spite of these important advantages, the spinal cord has received little attention in explorations of skill acquisition.

This general failure to consider and study the role of the spinal cord in skill acquisition has deep historical roots. The spinal cord was long thought to be simply a big well-protected nerve through which the brain interacts with the world (Liddell 1960, Neuburger 1981, Clarke & Jacyna 1987, Clarke & O'Malley 1996). In the 19th century, it was recognized as a waystation between the brain and the periphery that harboured a few simple reflexes; and in the 20th century it progressed to a repository of highly stereotyped behaviours such as locomotion. Nevertheless, it remained a hardwired structure that merely responded, albeit in intricate ways, to inputs from the brain and the periphery. This inferior status, which sharply distinguished the function of the spinal cord from the function of the brain, was clearly enunciated in the middle of the 19th century by the English neurologist Marshall Hall, and for reasons that were as much theological as scientific: the distinction protected the immortal soul, which was assumed to reside in the brain, from domination by the external world.

This prejudice persists into the present and underlies the minimal attention paid to the potential value of the spinal cord for the study of skill acquisition. Nevertheless, a number of studies over the past century produced intriguing evidence of spinal cord plasticity that might contribute to skill acquisition. For example, in the 1920s, Anna diGiorgio modified descending influence on the spinal cord by lesioning one side of the cerebellum in anaesthetized dogs, rabbits and guinea-pigs (DiGiorgio 1929, 1942). The initial effect was an asymmetric hindlimb posture: flexion in one leg and extension in the other. After a variable delay, she abolished the descending influence responsible for the asymmetry by transecting the thoracic spinal cord. When the delay was brief, the asymmetric posture disappeared. However, when the delay was longer the asymmetric posture persisted, even though all descending influence had been removed. Later work confirmed this finding, showed that it was not attributable to peripheral mediation (e.g. change in sensory receptor function), and defined its time course (Manni 1950, Gerard 1961, Chamberlain *et al.* 1963, Patterson 2001). The phenomenon, termed 'spinal fixation', was believed by Gerard and others to be an excellent model for the fixation or consolidation of memory. Other studies in the mid-20th century by John Eccles and others produced further evidence of activity-dependent spinal cord plasticity that could contribute to long-term behavioural change (Wolpaw & Carp 2006 for review). However, this evidence was not further explored as attention focused increasingly on simple invertebrate models and on hippocampus and other brain areas.

The simplest motor skill and the associated spinal cord plasticity

Spurred by the DiGiorgio work and encouraged by more recent evidence of short-term change in spinal cord reflex function (e.g. Hammond 1956), this laboratory set out in the late 1970s to develop a model for exploring skill acquisition that utilized the unique advantages of the spinal cord. The model is based on the spinal stretch reflex (SSR; produced mainly by the monosynaptic pathway composed of the primary afferent from the muscle spindle, its synapse on the motor neurone, and the motor neurone) and its electrical analogue, the H-reflex, which is evoked by direct electrical stimulation of the primary afferent (Magladery *et al.* 1951, Matthews 1972, Henneman & Mendell 1981, Brown 1984, Zehr 2002). While the pathway is wholly spinal, it is subject to descending influences from the brain that act directly on the motor neurone or on the primary afferent connection and can change SSR or H-reflex size. The goal was to develop a training paradigm that required continuous change in this descending influence. While the SSR normally occurs as a part of complex behaviours, it is in itself a simple behaviour, probably the simplest of which the mammalian CNS is capable; and adaptive changes in it are essentially simple skills [i.e. 'adaptive behaviours acquired through practice' (Compact OED 1993)] that can serve as laboratory models of the plasticity underlying skill acquisition. Operant conditioning of the SSR, or its electrical analogue the H-reflex, which has now been described in monkeys, humans, rats and mice, provides clear evidence of activity-dependent plasticity

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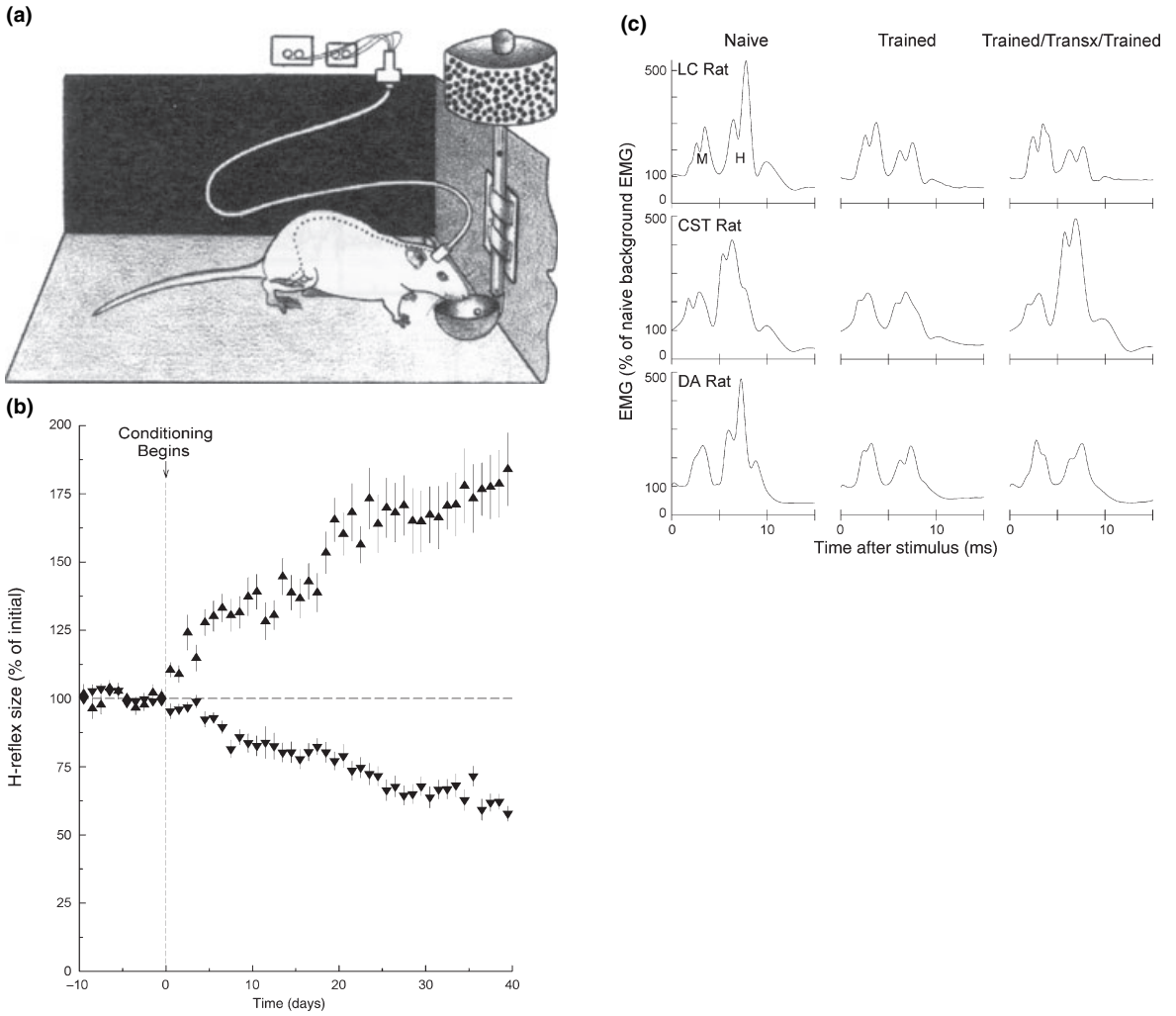

Figure 1 (a) The soleus electromyography (EMG) is monitored continuously in a rat with chronically implanted EMG electrodes and a tibial nerve cuff. Whenever its absolute value remains within a specified range for a randomly varying 2.3–2.7 s period, a nerve cuff stimulus elicits a threshold M response (i.e. a direct muscle response) and an H-reflex. For the first 10 days, the rat is exposed to the control mode, in which no reward occurs and the H-reflex is simply measured to determine its initial amplitude. For the next 50 days, it is exposed to the HR-up or HR-down mode, in which a food-pellet reward occurs if the H-reflex is above (HR-up) or below (HR-down) a criterion value. Background EMG and M response remain constant throughout. Successful conditioning, defined as a change of at least 20% in the correct direction, occurs in 80–90% of the animals. Their data are shown in (b). (b) The graph shows average daily H-reflexes (±SEM) from HR-up rats (up triangle, filled) and HR-down rats (down triangle, filled) for the control-mode exposure (i.e. days –10 to 0) and for the subsequent HR-up or HR-down mode exposure (i.e. days 0–40). Under the HR-up mode, the H-reflex rises gradually to about 175% of its initial value, while under the HR-down mode it falls gradually to about 60% (from Wolpaw 1997). (c) Average post-stimulus EMG from rats that underwent mid-thoracic transection of either: the lateral column [which includes rubrospinal, vestibulospinal and reticulospinal tracts (LC rat; top)]; the main corticospinal tract (CST rat; middle) or the dorsal ascending tracts (DA rats; bottom), for representative days before down-training of the soleus H-reflex (left), at the end of down-training and prior to transection (middle), and after transection and continued down-training (right). All three rats decreased the H-reflex (H) with down-training. LC or DA transection did not eliminate the H-reflex decrease. In contrast, CST transection led to loss of the H-reflex decrease and to an H-reflex even larger than the original, control-mode H-reflex. Background EMG (indicated by the value at time 0) and M response (M) remained stable throughout data collection (from Chen *et al.* 2002).

at particular sites in the spinal cord, and is elucidating the mechanisms and interactions of the spinal and supraspinal plasticity that underlies these simple skills (Wolpaw *et al.* 1983, Wolpaw 1987, Evatt *et al.* 1989, Chen & Wolpaw 1995, Wolf & Segal 1996, Segal 1997, Wolpaw & Tennissen 2001, Carp *et al.* 2006, Chen & Wolpaw 2005, Wolpaw & Chen 2006).

The standard rat version of this model is illustrated in Figure 1a. In the basic protocol, used in monkeys, humans, rats and mice, SSR or H-reflex size is measured

as electromyographic activity (EMG), and reward is given when the reflex size is greater than (for up-conditioning) or less than (for down-conditioning) a criterion. Because the protocol requires a stable level of background muscle tone, the reflex is elicited at an unpredictable time, and the reflex is the earliest possible CNS response, the animal or human can increase reward probability only by producing an appropriate steady-state change in the descending influence over the spinal arc of the reflex. Thus, the protocol operantly conditions appropriate change in this descending influence.

The basic experimental finding is that, after imposition of the reward criterion, reflex size changes appropriately over days and weeks (Fig. 1b). This adaptive change has two phases, a small rapid Phase 1 change in the first few hours or days, and a far slower Phase 2 change that continues to grow for weeks (Wolpaw & O'Keefe 1984, Chen *et al.* 2001). Phase 1 is thought to reflect rapid appropriate change in descending influence on the spinal reflex arc, while Phase 2 is thought to reflect the gradual spinal cord plasticity (see below) caused by the long-term continuation of the descending influence responsible for Phase 1. An extensive series of studies explored the effects on H-reflex conditioning of well-defined lesions of spinal cord descending pathways (Chen & Wolpaw 1997, 2002, Chen *et al.* 2006b). The results are unexpectedly clear: the critical descending influence, the input that produces reflex change, is carried by the corticospinal tract (CST); other major descending pathways are not needed. This finding is further supported by evidence that conditioning is possible in humans with partial spinal cord injuries, but does not occur in people with strokes involving sensorimotor cortex or in rats in which contralateral sensorimotor cortex has been ablated or the CST has been transected (Segal & Wolf 1994, Segal 1997, Chen *et al.* 2006a). For down-conditioning at least, the CST is essential both for acquisition of the skill and for its maintenance. If the CST is transected after down-conditioning has occurred, the conditioned reflex decrease disappears within 10 days (Chen & Wolpaw 2002). Figure 1c illustrates the dependence of down-conditioning on the CST.

The spinal cord plasticity associated with H-reflex conditioning is complex, involving alterations at multiple sites. Down-conditioning changes properties in the motor neurone cell body and axon (Carp & Wolpaw 1994, Halter *et al.* 1995, Carp *et al.* 2001a). These altered properties are manifested by a positive shift in motor neurone firing threshold and a fall in axonal conduction velocity. The most probable mechanism for both these changes is a positive shift in sodium channel activation voltage throughout the motor neurone (Halter *et al.* 1995). Together, the threshold change and an accompanying small decrease in excitatory postsynaptic potential (EPSP) size can largely explain the smaller reflex (Carp & Wolpaw 1994, Wolpaw 1997; Fig. 2a). Although activity-dependent synaptic plasticity has generally received the most attention, the existence and significance of plasticity in neuronal properties (e.g. in neuronal voltage-gated ion channels) is now apparent (Spitzer 1999, Cantrell & Catterall 2001, Carr *et al.* 2003). The positive shift in motor neurone firing threshold with H-reflex down-conditioning is an instance of such plasticity, and illustrates its behavioural significance. Physiological and anatomical studies suggest that SSR or H-reflex conditioning also alters the primary afferent-motor neurone synapse, other synaptic terminals on the motor neurone, motor unit properties and interneurones that convey oligosynaptic Group 1 input to the motor neurone (Carp & Wolpaw 1995, Feng-Chen & Wolpaw 1996, Carp *et al.* 2001b, Wang *et al.* 2006). For example, down-conditioning is accompanied by a large increase in the number of GABAergic terminals on the motor neurone (Fig. 2b; Wang *et al.* 2006). The relationship of this change to the conditioned decrease in the H-reflex remains to be determined.

New studies show that the cerebellum is essential for acquisition and long-term maintenance of H-reflex down-conditioning, probably through its connections to sensorimotor cortex, and suggest that the basal ganglia are also essential, at least for acquisition (Chen *et al.* 2004, Chen & Wolpaw 2005, Wolpaw & Chen 2006). The most remarkable finding concerns cerebellar involvement in maintenance of down-conditioning. If the cerebellar output nuclei dentate and interpositus are ablated after down-conditioning has occurred, the reflex decrease persists for 40 days and then rapidly disappears over about 10 days, leaving the rat with an H-reflex even larger than its control H-reflex was prior to down-conditioning. This surprising finding, combined with the fact that transection of the rubrospinal tract (which conveys cerebellar output to the spinal cord) does not impair conditioning, suggests that cortical plasticity induced and maintained by the cerebellum is responsible for the long-term survival of the spinal cord plasticity that is directly responsible for the altered H-reflex. Figure 2c summarizes current understanding of the hierarchy of spinal and supraspinal plasticity that appears to underlie the acquisition and maintenance of the ostensibly simple skill of H-reflex conditioning.

Activity-dependent spinal cord plasticity during normal life

The complex spinal cord plasticity associated with H-reflex conditioning is not merely a laboratory phenomenon. Gradual activity-dependent plasticity, driven

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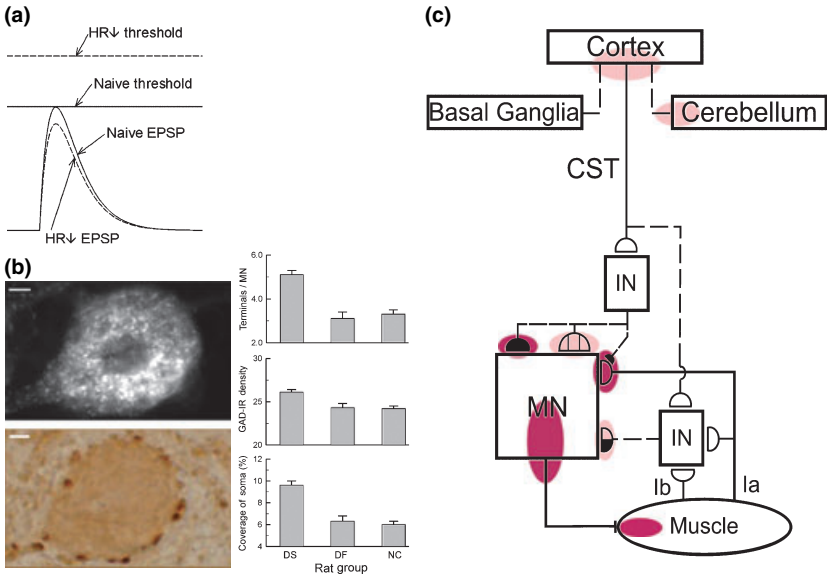

Figure 2 Operant conditioning of the spinal stretch reflex (SSR)/H-reflex pathway and the associated spinal and supraspinal plasticity. (a) Triceps surae motor neurones on the conditioned side of H-reflex down-conditioning (H_R) monkeys have more positive firing thresholds and slightly smaller Ia EPSPs. These two findings together can explain the smaller H-reflex (from Wolpaw 1997). (b) Effects of successful down-conditioning on GABAergic terminals in soleus motor neurones [assessed by glutamic acid decarboxylase (GAD^{67})-immunoreactivity (GAD-IR)]. Top left: soleus motor neurone labelled by Alexa-Fluor-488 conjugated with CTB injected in the muscle; bottom left: same motor neurone showing GAD-IR (i.e. GABAergic) terminals (dark) on the periphery of the motor neurone (bars = 5 μm); right: average (±SEM) values for down-conditioning successful (DS), down-conditioning failed (DF), and naive control (NC) rat groups for: number of GABAergic terminals/motor neurone; terminal GAD density and GABAergic terminal coverage of soma (in per cent of perimeter; $***P < 0.001$; compared with the NC group). After successful down-conditioning, soleus motor neurones have more GABAergic terminals, and these terminals are more densely labelled and cover more of the soma (from Wang *et al.* 2006). (c) Spinal and supraspinal sites (shaded ovals) of plasticity accompanying operant conditioning of the SSR or its electrical analogue, the H-reflex. 'MN' is the motor neurone, 'CST' is the main corticospinal tract and each 'IN' is one or more spinal interneurons. Open synaptic terminals are excitatory, solid ones are inhibitory, half-open ones could be either, and the subdivided one is a cluster of C-terminals. Dashed pathways indicate the possibility of intervening spinal interneurons. The monosynaptic (and probably oligosynaptic) SSR/H-reflex pathway from Ia and Ib afferents to the motor neurone is shown. The definite (heavy shading) or probable (light shading) sites of plasticity include: the motor neurone membrane (i.e. firing threshold and axonal conduction velocity), motor unit properties, C-terminals on the motor neurone, the Ia afferent synaptic connection, terminals conveying disynaptic group I inhibition or excitation to the motor neurone, sensorimotor cortex (or closely associated areas) and cerebellum (or its nuclei). The essential roles of the CST (originating in sensorimotor cortex) and of cerebellar output to cortex are indicated (updated from Wolpaw 1997).

by descending and associated peripheral inputs, shapes spinal cord function during development and continues to adjust it throughout later life. This plasticity establishes and maintains spinal cord function in a state that supports effective motor behaviours.

Early in life, descending input to the spinal cord helps to induce the plasticity that leads to an adult spinal cord that has normal reflex patterns, supports standard motor skills like locomotion, and can also support specialized skills like dancing or playing the piano. Among the most fundamental and important reflexes are those that produce rapid withdrawal from painful stimuli. They are acquired early in life. In the neonatal rat, focal nociceptive stimulation produces diffuse and often inappropriate muscle excitation and limb movement. In contrast, in the normal adult, this stimulation activates only the appropriate muscles, i.e. those that withdraw the limb from the painful stimulus.

Descending input during early life is essential for shaping these appropriate adult flexion withdrawal reflexes (Levinsson *et al.* 1999, Waldenstrom *et al.* 2003). When neonatal spinal cord transection at birth abolishes descending influence, the adult pattern does not develop, and inappropriate withdrawal reflexes persist in the adult (Fig. 3a). Peripheral input is also important for development of normal flexion withdrawal responses. Peripheral anaesthesia during development prevents this development.

Spinal cord proprioceptive reflexes (e.g. the SSRs) contribute to locomotion and other motor behaviours (Rossignol 1996). In human neonates, muscle stretch produces SSRs in both the stretched muscles and their

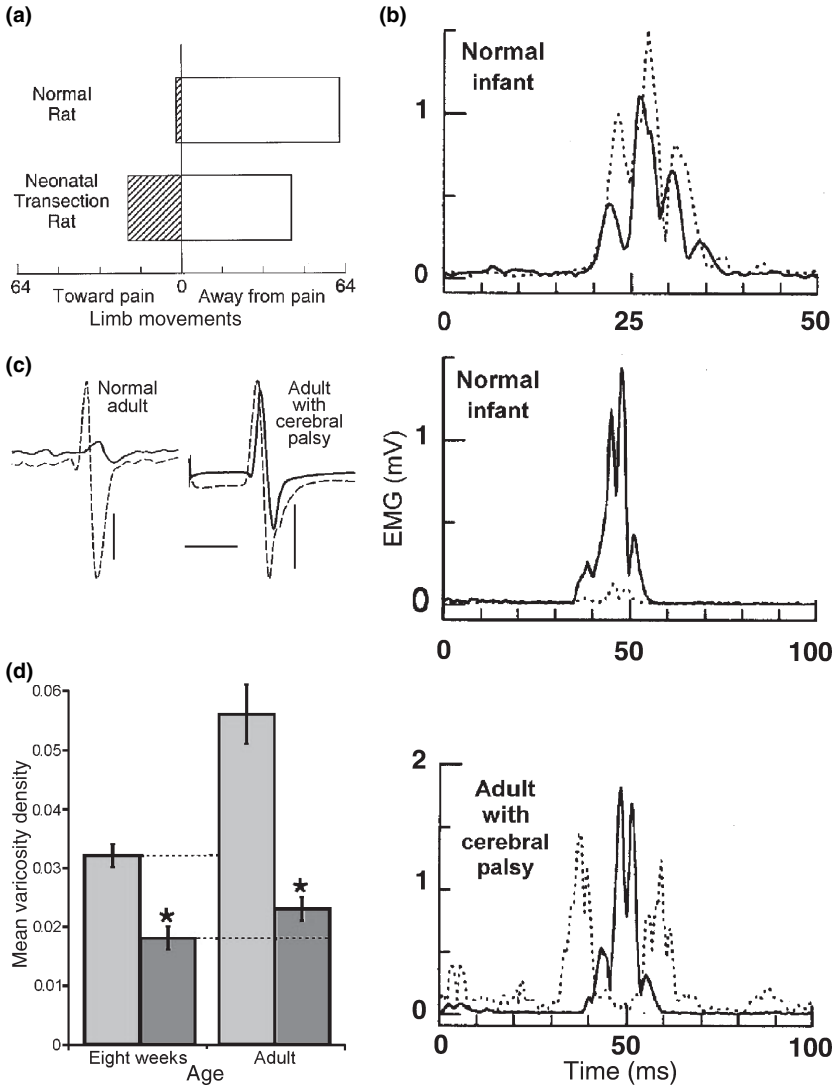

Figure 3 Activity-dependent spinal cord plasticity during development. (a) Direction of limb movement caused by flexion withdrawal responses to a nociceptive stimulus in normal adult rats and in adult rats in which the spinal cord was transected just after birth. The direction is nearly always appropriate, i.e. away from the painful stimulus, in normal adults, but it is often inappropriate in transected adults. Neonatal transection prevents the normal shaping of flexion withdrawal reflexes by descending input (modified from Levinsson *et al.* 1999). (b) Short-latency electromyographic (EMG) responses of soleus (solid) and tibialis anterior (dotted) muscles to sudden foot dorsiflexion, which stretches the soleus and shortens the tibialis anterior, in a normal infant, a normal adult and an adult with cerebral palsy. In the normal infant, spinal stretch reflexes are evident in both muscles. In the normal adult, a reflex occurs only in the stretched muscle, i.e. the soleus, while little or no response occurs in the tibialis anterior. In contrast, in the adult with cerebral palsy, in whom perinatal supraspinal injury has impaired descending input, the infantile pattern persists: reflexes are evident in both muscles (from B. Myklebust, unpublished data; Myklebust *et al.* 1982, 1986 for comparable data). (c) Ipsilateral (solid) and contralateral (dashed) EMG responses (first dorsal interosseus muscle) to transcranial magnetic stimulation over motor cortex in a normal adult (left) and an adult with cerebral palsy (right). Horizontal scale bar is 20 ms, vertical bar is 200 μV. The large ipsilateral response in the adult with cerebral palsy indicates abnormal preservation of the strong ipsilateral corticospinal connections that normally disappear early in life (modified from Eyre *et al.* 2001). (d) Densities in 8-week-old adult cats of putative corticospinal tract (CST) boutons (varicosities) in cervical spinal cord ipsilateral (dark grey) and contralateral (light grey) to forelimb muscle that had been paralyzed from age 3 to 7 weeks. Muscle paralysis during development reduces CST innervation. This deficit lasts into adulthood. Asterisks mark significant differences from the other side of the spinal cord (i.e. from the side contralateral to the paralyzed muscle; modified from Martin *et al.* 2004).

antagonists (Myklebust *et al.* 1986, Wolpaw 1997, O'Sullivan *et al.* 1998). As Figure 3b illustrates, the antagonist SSRs disappear during childhood, and the adult has only standard 'knee-jerk' reflexes confined to the stretched muscles. However, if perinatal supraspinal damage (e.g. cerebral palsy) disrupts descending input,

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this evolution may not occur, and antagonist SSRs may persist in adulthood and contribute to disability.

Descending activity early in life is also important for urinary function. Voiding is easily evoked in neonates by peripheral stimulation of a spinal reflex arc. In subsequent development, this reflex voiding is suppressed and brain control of voiding becomes dominant. This evolution appears to depend on change in the relative strengths of peripheral and descending excitatory inputs to spinal cord pre-ganglionic neurones responsible for voiding (de Groat 2002, Vizzard 2006). Neonatal spinal cord transection prevents this evolution, so that infantile reflex voiding remains in the adult. After spinal cord injury in adults, the infantile pattern may reappear.

During development, the CST to provide the normal adult pattern of largely contralateral innervation (Eyre *et al.* 2001, Eyre 2003, ten Donkelaar *et al.* 2004, Martin 2005). Early damage to sensorimotor cortex of one hemisphere can prevent this evolution, and produce an abnormal adult pattern in which the undamaged side projects strongly to both sides of the spinal cord (Fig. 3c). The abnormality appears to come from absence of the normal activity-dependent competition of ipsilateral and contralateral connections (Eyre *et al.* 2001). It may be accompanied by effects on muscle afferent connections in the spinal cord and in spinal neuronal properties (e.g. expression of parvalbumin and the early immediate gene c-Jun; Gibson *et al.* 2000). The eventual functional impact is especially severe in humans, in whom corticospinal connections are normally important for movement control (Eyre *et al.* 2000, Mayer & Esquenazi 2003). The motor abnormalities may be modest in the infant and only become prominent later on, as complex motor skills do not develop normally. Abnormal peripheral input during development due to paralysis of a particular muscle may also lead to adult abnormalities in corticospinal motoneuronal connections (Fig. 3d) and in motor control (Martin *et al.* 2004).

Mastery of motor skills later on in life is associated with changes in spinal cord reflexes. Numerous studies show that spinal reflexes are affected by the nature, intensity and duration of past physical activity and by specific training regimens. SSRs and H-reflexes are different in athletes and non-athletes and among different kinds of athletes (Rochcongar *et al.* 1979, Goode & Van Hoven 1982, Casabona *et al.* 1990, Koceja *et al.* 1991, 2004, Nielsen *et al.* 1993, Augé & Morrison 2000). Nielsen *et al.* (1993) measured soleus H-reflexes in people who were sedentary, moderately active or extremely active, and also in professional ballet dancers. H-reflexes and disynaptic reciprocal inhibition were larger in people who were moderately active than in those who were sedentary, and even larger in those who were extremely active. As human soleus comprises mainly slow (i.e. type I) fibres, exercise-induced alteration in motor unit properties probably cannot account for these differences associated with activity. The most striking finding was that both the H-reflex and disynaptic reciprocal inhibition were smallest of all in professional dancers, who were far more active than any other group (Fig. 4a). Knowing that muscle co-contraction is associated with increased pre-synaptic inhibition and decreased reciprocal inhibition, the authors hypothesized that the prolonged co-contractions essential in the classical ballet postures produced lasting decreases in transmission at primary afferent synapses, and thus smaller H-reflexes and weaker reciprocal inhibition. From the perspective of performance, the lessened peripheral influence on motor neurones indicated by the smaller reflexes might increase cortical control and thereby improve the precision of movement.

In studying people with differing histories of physical activity, it is hard to eliminate the possible confounding factor of differences in basic genetic endowments. Prospective investigations of the impact of specific training regimens can avoid this problem; and they furnish additional evidence of activity-dependent spinal cord plasticity. In one study, monkeys learned to make smooth repetitive flexion and extension movements about the elbow, while random brief perturbations were superimposed (Meyer-Lohmann *et al.* 1986). Over months and years, the SSR produced by the perturbation gradually grew to take over the task of counteracting the perturbation, and longer-latency reflexes gradually waned (Fig. 4b). The larger SSR appeared to be adaptive, for it was associated with faster elimination of the trajectory deviation caused by the perturbation. The authors concluded that the results 'demonstrate a growing role for fast segmental mechanisms in the reaction to external disturbances as motor learning progresses'.

Studies in humans report reflex changes developing over days and weeks in response to particular training regimens (Pérot *et al.* 1991, Voigt *et al.* 1998, Yamanaka *et al.* 1999, Schneider & Capaday 2003). Practice of a backward-walking task (15 min/day) led to a gradual change in the relationship between soleus H-reflex size and the time in the step cycle when the reflex was evoked.

On the first day, the reflex was large well before the beginning of the soleus burst in the stance phase of the cycle. By the 10th day, the H-reflex was not detectable until the burst began (Fig. 4c). The earlier reflex increase on the first day may compensate for uncertainty as to when the stance phase, with its need for greater soleus activity, will begin. The increased sensitivity of the reflex arc promotes rapid excitation by foot contact. The time of contact becomes more predictable as training progresses, so that this compensation is not necessary.

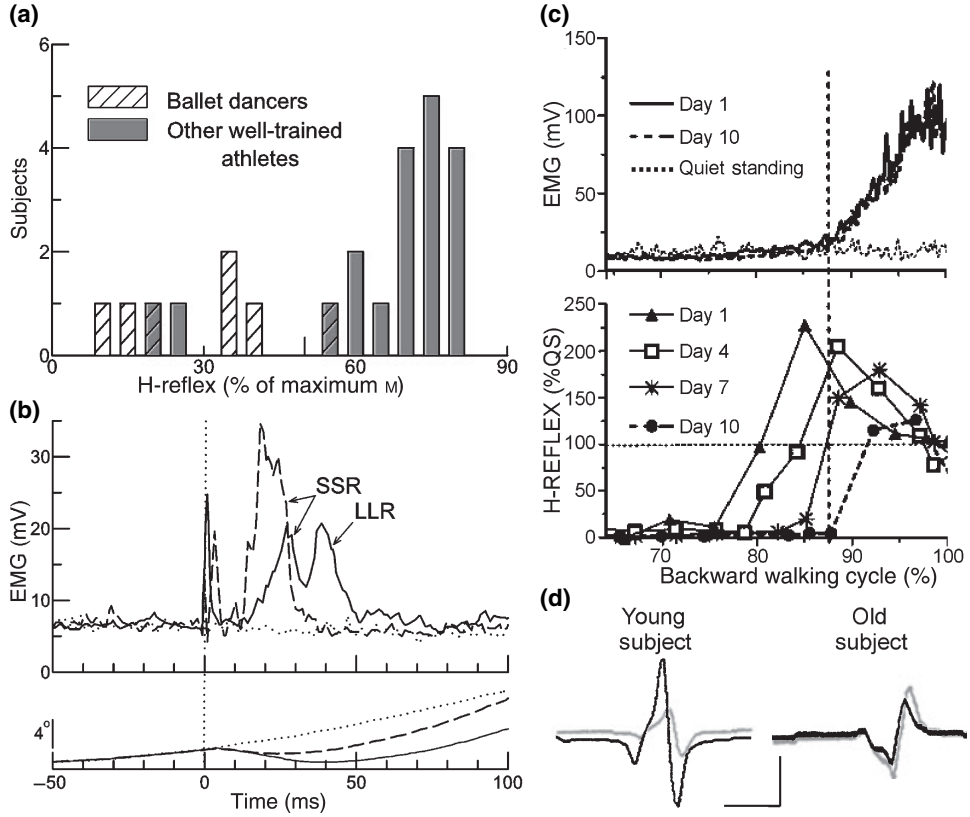

Figure 4 Activity-dependent spinal cord plasticity accompanying skill acquisition and with ageing. (a) Soleus H-reflexes are much smaller in professional ballet dancers than in other well-trained athletes (e.g. runners, swimmers, cyclists; H-reflexes of sedentary subjects are in between; modified from Nielsen *et al.* 1993). (b) Working for reward, monkeys performed an elbow flexion–extension task on which brief perturbations were superimposed at random times. Biceps electromyography (EMG) and elbow angle (flexion upward) for an unperturbed trial (dotted), a perturbed trial early in training (solid), and a perturbed trial late in training (dashed) are shown. Early in training, perturbation elicits both a spinal stretch reflex (SSR) and a long-latency polysynaptic response (LLR). After intermittent training over several years, the SSR is much larger and the LLR is gone. The SSR has gradually taken over the task of opposing the perturbation. This improves performance: the disturbance in the normal course of elbow flexion is smaller and briefer (modified from Meyer-Lohmann *et al.* 1986). (c) Change in soleus H-reflex size as a function of time in the backward-walking step cycle as a subject learns backward-walking over 10 days. Top: soleus EMG on days 1 and 10 just before and after onset of the soleus burst associated with the stance phase of the step cycle. The dotted line shows soleus EMG for quiet standing. Bottom: H-reflex size (in per cent of size during quiet standing) vs. time in the backward-walking step cycle for training days 1, 4, 7 and 10. Soleus EMG does not change with training. In contrast, the prominent increase in H-reflex size prior to the soleus burst onset (vertical dashed line) seen on day 1 is gone by day 10. (d) Soleus H-reflexes in prone (black) and standing (grey) positions from a young person and from an old person. In old subjects, the H-reflex tends to be smaller and less affected by body position. Scale bars are 10 ms and 2 mV (modified from Koceja *et al.* 1995).

The reflex changes associated with ageing are additional evidence of adaptive spinal cord plasticity in adult life and in response to specific demands (Sabbahi & Sedgwick 1982, DeVries *et al.* 1985, Koceja *et al.* 1995, Morita *et al.* 1995, Angulo-Kinzler *et al.* 1998, Koceja & Mynark 2000, Zheng *et al.* 2000, Scaglioni *et al.* 2003, Kido *et al.* 2004). The age-related alterations in reflex size and task-dependent modulation reported in these studies (e.g. Fig. 4d) are likely to reflect both the direct and indirect impact of ageing, i.e. the direct impact of ageing on the reflex circuitry itself and the indirect impact of ageing due to its effects elsewhere in the CNS or on the peripheral sensory and motor apparatus involved in movement.

Activity-dependent spinal cord plasticity and its relations to behavioural change

The phenomena summarized here indicate that changes in spinal cord reflexes accompany the acquisition and maintenance of motor skills throughout life. The complex pattern of spinal and supraspinal plasticity that accompanies acquisition of the simplest skill, H-reflex increase or decrease, implies that other motor

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skills involve even more complex multisite plasticity. This multisite plasticity is consistent with the growing evidence that activity-dependent plasticity is ubiquitous in the CNS and occurs with even the simplest learning in both invertebrates and vertebrates (Wolpaw & Lee 1989, Carrier *et al.* 1997, Cohen *et al.* 1997, Lieb & Frost 1997, Thompson *et al.* 1997, Whelan & Pearson 1997, Lisberger 1998, Garcia *et al.* 1999, Hansel *et al.* 2001, King *et al.* 2001, Wolpaw & Tennissen 2001, van Alphen & De Zeeuw 2002, Medina *et al.* 2002, Vaynman & Gomez-Pinilla 2005, Van Alphen & De Zeeuw 2002, Vaynman & Gomez-Panilla 2005, Wolpaw 2006).

Because the function of the CNS is to produce appropriate behaviors and because activity-dependent plasticity is ubiquitous in the CNS, complex plasticity with even simple behaviours is both necessary and inevitable, especially in the spinal cord.

The spinal cord (and its homologous brainstem nuclei) constitute the final assembly point for neuromuscular behaviours, both simple and complex. The spinal cord assembles and executes the end products of activity elsewhere in the CNS. Thus, the motor neurones, interneurons and synapses in the lumbosacral spinal cord produce all the numerous varieties of locomotion and postural maintenance withdraw the legs from pain, participate in actions that engage all four limbs, support bladder and bowel function, and execute many specialized actions. The fact that the spinal cord maintains these many different behaviours and continues to add new ones throughout life, implies that its neurones and synapses are constantly adjusted and readjusted to support the current behavioural repertoire. Such adjustments take place in the short-term as the organism changes from one behaviour to another or passes through the different phases of a single behaviour. For example, pre-synaptic inhibition at the primary afferent synapse on the motor neurone changes from standing to walking to running, and responses to primary afferent input change over the step cycle (Capaday & Stein 1987, Stein 1995, Faist *et al.* 1996, Rossignol 1996, Pearson & Ramirez 1997, Zehr 2002). In addition, as the data summarized above imply, over the long-term gradual activity-dependent plasticity, initiated and guided by descending and peripheral inputs, serves to maintain the spinal cord in a state suited to its current behavioural roster. This long-term control, which reflects a consensus of the different patterns of activity accompanying the different behaviours, appears to operate as a coarse adjustment, defining ranges within which the adjustments specific to each behaviour occur. For example, at one time, the strength of primary afferent input to soleus motor neurones is capable of varying over a range that includes values suited for standing, walking and running (Zehr 2002).

In this context, the neural activity that adds a new behaviour to the repertoire is likely to induce not only the plasticity that supports the new behaviour, but also, in addition, plasticity that maintains the old behaviours. This is likely whether the activity is due to daily practice and the behaviour is a new motor skill or the activity comes from peripheral or central damage and the behaviour represents or compensates for a functional abnormality. For example, the greater motor neurone excitation by primary afferent input that underlies soleus H-reflex up-conditioning affects other behaviours to which that input contributes, such as the soleus locomotor burst (Chen *et al.* 2005a; Fig. 5). This impact may spur further 'compensatory' activity-dependent plasticity that preserves these older behaviours.

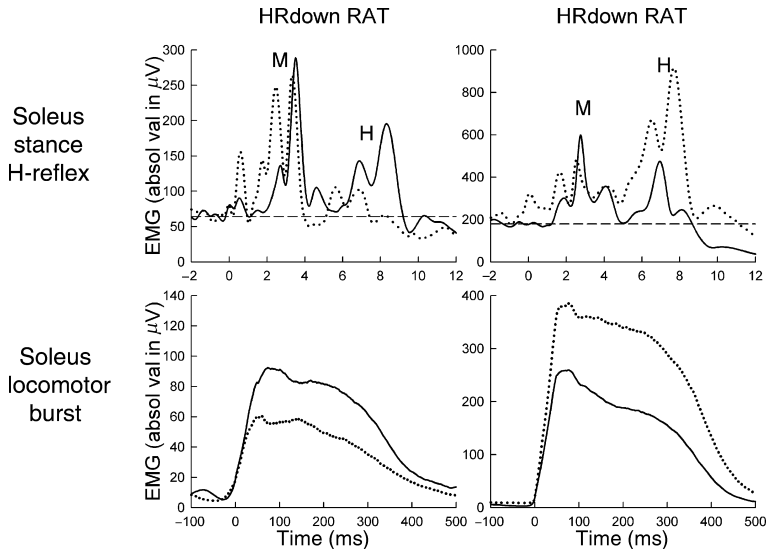

Figure 5 Soleus H-reflexes in the stance phase of locomotion and right soleus bursts in undisturbed locomotion before (solid) and after (dotted) conditioning from a down-conditioned (HR-down) and an up-conditioned (HR-up) rat. Each stance H-reflex is the average of 109–166 trials, and each burst is the average of 131–462 bursts. After conditioning, both the soleus stance H-reflex and the soleus locomotor burst are smaller in the HR-down rat and larger in the HR-up rat (from Chen *et al.* 2005a).

The still mysterious plasticity that ensures a normal contralateral H-reflex in a monkey after H-reflex down-conditioning (Wolpaw & Lee 1989, Wolpaw *et al.* 1993) may be compensatory, helping to maintain normal contralateral function. Furthermore, because activity-dependent plasticity can occur at many places in the spinal cord, the changes in activity resulting from the plasticity responsible for a new behaviour or for preserving old behaviours are likely to produce further 'reactive' plasticity in other places. For example, the smaller stretch reflexes in the ostensibly normal arm contralateral to an arm paralyzed by a hemispheric stroke (Thilmann *et al.* 1990), may reflect reactive plasticity caused by altered activity in the pathways that connect the two sides of the spinal cord.

These factors suggest that mastery of a new skill involves three classes of plasticity: primary plasticity that underlies the new behaviour, compensatory plasticity that maintains old behaviours in spite of the effects of the primary plasticity and reactive plasticity that results from modifications in activity caused by the primary and compensatory plasticity. This aetiological classification accounts for the complex multisite plasticity that is associated with even the simplest skill (e.g. H-reflex conditioning). It implies that multisite plasticity is necessary, to maintain the full behavioural repertoire, as well as inevitable, due to the ubiquity of activity-dependent plasticity in the CNS. It also appears to explain why some examples of plasticity [e.g. the contralateral spinal cord plasticity with H-reflex conditioning (Wolpaw & Lee 1989)] have no obvious relationship to the behavioural change with which they are associated.

The activity-dependent spinal cord plasticity that occurs during development and during skill acquisition later on is largely created and guided by descending input from the brain, often in association with peripheral input. As the plasticity associated with H-reflex conditioning illustrates (Fig. 2c), this descending influence is likely to be associated with and may depend on plasticity in cortex, cerebellum or other brain areas. The behavioural effects accompanying spinal cord plasticity appear to reflect the complex interactions of plasticity at multiple spinal and supraspinal sites (Carrier *et al.* 1997, Whelan & Pearson 1997, Wolpaw & Tennissen 2001, Wolpaw & Chen 2006).

Significance of activity-dependent spinal cord plasticity

The spinal cord's clear capacity for activity-dependent plasticity implies that many motor skills, particularly those acquired through prolonged practice, involve spinal cord plasticity. This implication is consistent with the impressive evidence that activity can slowly change the spinal cord, and with the lengthy periods of practice required for mastery of athletic skills and other skills like playing a musical instrument. Indeed, these skills probably cannot be fully understood by studying only plasticity in cortex, cerebellum or other brain areas. The plasticity in the spinal cord must also be explored. This requirement is often ignored in studies focused on the role of cortical plasticity in explaining changes in behaviour. The fact that spinal cord plasticity can, and often does contribute to behavioural changes certainly complicates the study of such changes. Nevertheless, without appropriate recognition of and attention to spinal cord plasticity, attempts to define how CNS plasticity explains behavioural change are likely to produce incomplete or even misleading insights.

Furthermore, the fact that motor skills involve multisite and multilevel (i.e. spinal and supraspinal) plasticity suggests that intellectual skills, such as language mastery or mathematical facility, depend on widely distributed plasticity. The swift behavioural changes that often engage the most attention, such as single-trial acquisition of a new word, may simply reflect minor adjustments in patterns of plasticity gradually created by prolonged practice, adjustments analogous to the change in pre-synaptic inhibition with the transition from standing to running or the change in descending input responsible for Phase 1 change in the SSR (see above). Thus, the elucidation of many skills may depend on the study of gradually acquired activity-dependent plasticity in the brain comparable with that found to occur in the spinal cord. Indeed, such studies might best start with simple motor skills and with the spinal cord, for its comparative simplicity and accessibility and its well-defined connections with the brain facilitate explorations of activity-dependent plasticity and of the ways in which multiple sites of plasticity interact to produce new skills.

Clinical use of activity-dependent spinal cord plasticity

Activity-dependent spinal cord plasticity and its interactions with plasticity elsewhere in the brain are important not only in normal motor behaviours, but also in the complex motor disabilities that accompany spinal cord injuries and other chronic neurological disorders. Recognition of this additional importance has coincided with and has been encouraged by the energy and optimism now focused on efforts to restore spinal cord structure and function after injury (e.g. Dobkin & Havton 2004, Liverman *et al.* 2005, Merzenich 2006). Expectations for achieving regeneration of pathways and neurones that have been damaged or lost inevitably raise the issue of how regenerated spinal cord is to

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become functional. As discussed above, an effective adult spinal cord is the product of appropriate activity-dependent plasticity during development and throughout later life. A freshly (and probably only partially), regenerated spinal cord will almost certainly not function well (Muir & Steeves 1997); it is likely to display diffuse infantile reflexes and other disordered and ineffective behaviours. As a result, when techniques for inducing spinal cord regeneration are available, new rehabilitation techniques for properly re-educating the regenerated spinal cord will probably be essential. This anticipated need is spurring attention to activity-dependent spinal cord plasticity. Understanding this plasticity is essential for understanding both the changes caused by injury and the processes that might be engaged and guided to restore effective function.

In developing new rehabilitation techniques for long-term neuromuscular disorders such as spinal cord injury, the spinal cord's capacity for activity-dependent plasticity is at the same time both a challenge and an opportunity. This capacity could contribute to the disabilities associated with spinal cord injury and will doubtless affect the outcomes of new therapies that produce regeneration of spinal cord pathways and neurones. At the same time, it provides an opportunity to induce and guide recovery of function, and could allow incomplete regeneration to support substantial functional improvement. For these reasons, the productive engagement of activity-dependent spinal cord plasticity will probably be a key element in new rehabilitation protocols for people with spinal cord injuries or other chronic neuromuscular disorders. Successful initiation and guidance of activity-dependent spinal cord plasticity will require training protocols that create appropriate patterns of peripheral and descending inputs to the spinal cord. The development of such methods has begun for locomotion (Shurrager & Dykman 1951, Lovely *et al.* 1986, Barbeau & Rossignol 1987, Barbeau *et al.* 2002, Rossignol *et al.* 2002, 2004, Tillakaratne *et al.* 2002, Edgerton *et al.* 2004, Brown 2006, Rossignol 2006), while other important behaviours (e.g. urination) have yet to be addressed.

A recent series of studies (Chen *et al.* 2005a,b) examines the possibility that operant conditioning of the H-reflex or other spinal cord reflexes might be used to produce spinal cord plasticity that improves the performance of other behaviours. The first study, conducted in normal rats, sought to determine whether soleus H-reflex conditioning affects locomotion. The results were clear. In rats in which the right H-reflex was increased by up-conditioning, the right soleus locomotor burst also became larger; and in rats in which the right H-reflex was decreased by down-conditioning, the right soleus locomotor burst also became smaller. These effects are consistent with the known importance of primary afferent input in producing the locomotor burst (Capaday & Stein 1987, Stein 1995, Faist *et al.* 1996, Rossignol 1996, Pearson & Ramirez 1997, Zehr 2002). At the same time, these effects on soleus participation in locomotion were not accompanied by changes in locomotion itself, i.e. in stride length or right–left symmetry. It appears that, in these normal rats, compensatory changes in the locomotor activity of other muscles maintained locomotion unchanged in spite of the effects of H-reflex conditioning on soleus motor neurone response to primary afferent input.

The second study (Chen *et al.* 2005b) explored the effects of H-reflex conditioning on locomotion in spinal cord-injured rats. It tested the hypothesis that an appropriate conditioning protocol can improve locomotion in spinal cord-injured rats. Mid-thoracic transection of the right lateral column (LC) produced a lasting asymmetry in treadmill locomotion. The right stance phase was abnormally short, so that the rats limped. Then, the rats were either exposed or not exposed to an H-reflex up-conditioning protocol that increased right soleus response to primary afferent input, and locomotion was tested again. H-reflex up-conditioning, which strengthened the right soleus burst, abolished the locomotor asymmetry. In contrast, the asymmetry persisted in the unconditioned rats. These results suggest that reflex conditioning protocols could improve motor function in people with partial spinal cord injuries. Such protocols could be particularly valuable when regeneration becomes practical and precise techniques for re-educating the regenerated spinal cord are needed in order to restore useful function. Another recent study demonstrates conditioning of reciprocal inhibition in the rat, and thus extends the options for using reflex conditioning to change motor function (Chen *et al.* 2006c).

These endeavours will encounter the complexity of the activity-dependent plasticity associated with even the simplest training protocols (e.g. Fig. 2c). They must also accommodate a distinctive feature of activity-dependent spinal cord plasticity as it functions in normal life and in response to disease: the slow rate of its impact on behaviour. Despite the rapidity of activity-dependent processes such as LTP, which is known to occur in the spinal cord (Liu & Sandkühler 1997, Ji *et al.* 2003), the behavioural changes resulting from activity-dependent spinal cord plasticity develop gradually. This gradual course is presumably due to the fact that each behavioural change is the product of multiple activity-dependent mechanisms and that these multiple mechanisms reflect continuing interaction and competition among the adaptive demands of numerous behaviours, old as well as new.

Reflex changes during development and those associated with skills such as ballet occur over months and

 doi: 10.1111/j.1748-1716.2006.01656.x

years; and those resulting from H-reflex operant conditioning or other specialized training regimens take days and weeks at least. While the H-reflex and other reflexes can differ substantially across different behaviours [e.g. standing and running (Zehr 2002)], or even between the different phases of a single behaviour [e.g. stance and swing phases of walking (Faist *et al.* 1996)], the specification of the reflex strengths during a particular behaviour develops gradually. This feature is probably fortunate – rapid major changes in reflexes that are independent of the contexts of specific behaviours could greatly disturb motor control and require prodigious compensation by the brain.

The characteristically gradual effect of activity-dependent spinal cord plasticity on behaviour indicates that research studies and clinical applications should extend over sufficient periods of time. In addition, the ubiquity of activity-dependent plasticity and the complex interactions among primary, compensatory and reactive plasticity, mean that functional effects are likely to evolve over time. Early improvements will not always evolve into long-term gains; and, conversely, early deleterious impact may give way to long-term benefit.

Dr Ann M. Tennissen gave invaluable assistance in the preparation of the manuscript. Work in the author's laboratory has been supported by NIH (NS22189 and HD36020), The United Cerebral Palsy Research and Educational Foundation, The Paralyzed Veterans of America, The International Spinal Research Trust and The Christopher Reeve Paralysis Foundation.

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