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ACTIVITY-DEPENDENT SPINAL CORD PLASTICITY IN HEALTH AND DISEASE

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■ **Abstract** Activity-dependent plasticity occurs in the spinal cord throughout life. Driven by input from the periphery and the brain, this plasticity plays an important role in the acquisition and maintenance of motor skills and in the effects of spinal cord injury and other central nervous system disorders. The responses of the isolated spinal cord to sensory input display sensitization, long-term potentiation, and related phenomena that contribute to chronic pain syndromes; they can also be modified by both classical and operant conditioning protocols. In animals with transected spinal cords and in humans with spinal cord injuries, treadmill training gradually modifies the spinal cord so as to improve performance. These adaptations by the isolated spinal cord are specific to the training regimen and underlie new approaches to restoring function after spinal cord injury. Descending inputs from the brain that occur during normal development, as a result of supraspinal trauma, and during skill acquisition change the spinal cord. The early development of adult spinal cord reflex patterns is driven by descending activity; disorders that disrupt descending activity later in life gradually change spinal cord reflexes. Athletic training, such as that undertaken by ballet dancers, is associated with gradual alterations in spinal reflexes that appear to contribute to skill acquisition. Operant conditioning protocols in animals and humans can produce comparable reflex changes and are associated with functional and structural plasticity in the spinal cord, including changes in motoneuron firing threshold and axonal conduction velocity, and in synaptic terminals on motoneurons. The corticospinal tract has a key role in producing this plasticity. Behavioral changes produced by practice or injury reflect the combination of plasticity at multiple spinal cord and supraspinal sites. Plasticity at multiple sites is both necessary—to insure continued performance of previously acquired behaviors—and inevitable—due to the ubiquity of the capacity for activity-dependent plasticity in the central nervous system. Appropriate induction and guidance of activity-dependent plasticity in the spinal cord is an essential component of new therapeutic approaches aimed at maximizing function after spinal cord injury or restoring function to a newly regenerated spinal cord. Because plasticity in the spinal cord contributes to skill acquisition and because the spinal cord is relatively simple and accessible, this plasticity is a logical and practical starting point for studying the acquisition and maintenance of skilled behaviors.

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INTRODUCTION

The Cinderella of the Central Nervous System

As the title of this section implies, the spinal cord has always occupied a humble place in neuroscience (Aminoff 1993). Considered part of the central nervous system (CNS) by virtue of its meningeal coverings and histology, it is commonly thought to be merely a waystation between the brain and the periphery, the home of a few hardwired reflexes and nothing else. This traditional view goes back 1800 years to Galen, who wrote that the spinal cord was essentially a protected bundle of nerves that connect the brain to the body (see Liddell 1960, Neuburger 1981, Clarke & Jacyna 1987, Clarke & O'Malley 1996 for historical review). Even its reflex functions went unrecognized until well after the Renaissance. Reflexes were believed to be entirely peripheral, produced by activity that passed from sensory receptors to muscles through anastomoses between peripheral nerves, without the participation of the brain or spinal cord. Pliny the Elder, who predated Galen, knew that this was not true, and so did Leonardo da Vinci and Stephen Hales later on, but the idea persisted until the eighteenth century, when Robert Whytt, studying the headless frog, observed that "the strong convulsive motions excited by irritation in the legs and trunk. . . cease as soon as [the spinal cord] is destroyed."

While Whytt laid to rest the Galenic belief that the spinal cord was only a big nerve, subsequent developments led to a distinction between the spinal cord and the brain that is still widely accepted and maintains the spinal cord's inferior status. In the early nineteenth century Marshall Hall distinguished between "The Cerebral, or the Sentient and Voluntary" part of the nervous system and the "True Spinal, or the Excito-motory" part. The first was the cerebral hemispheres and cerebellum and produced conscious, or volitional, behavior; the second was the spinal cord and medulla and produced reflexes. Hall thought these two systems were totally separate and even had separate sets of afferent and efferent nerves. His reasons were both scientific and religious: The separation protected the immortal soul, which resided in the brain, from domination by the external world. He coined the term "reflex arc" to describe the pathways underlying the fixed behaviors ascribed to the spinal cord.

Hall's theory of the spinal cord as a reflex center underlies current concepts. While we now know that spinal reflex pathways do not have a separate set of peripheral nerves, most neuroscientists retain something like Hall's distinction between the voluntary behaviors produced by the brain and the involuntary, or reflex, behaviors produced by the spinal cord. The spinal cord is often conceived to be a hardwired system that simply responds quickly and in a stereotyped, or "knee-jerk" fashion to afferent inputs from sensory receptors in the periphery or to descending commands from the brain. For example, sudden muscle stretch produces rapid contraction of the stretched muscle and ascending activity in dorsal column pathways, a pinprick to the foot causes rapid limb withdrawal nearly as quickly, and descending activity from motor cortex rapidly excites spinal motoneurons and produces muscle

contraction. Such short-latency input-output connections are traditionally believed to be the full extent of the spinal cord's capabilities. Activity-dependent plasticity—defined as persistent CNS modification that results from past experience and affects future behavior—is considered a supraspinal capacity. Complex motor performances—standard skills such as walking and writing and special skills such as dancing and piano playing—that are acquired through practice, and thus reflect the persistent effects of activity, are generally thought to result from supraspinal plasticity that simply uses the fixed capacities of the unchanging spinal cord.

Activity-Dependent Plasticity in the Spinal Cord

This traditional view ignores a large body of evidence that has accumulated over the past century and grown rapidly in recent years. Both clinical and experimental observations indicate that the spinal cord, like other parts of the CNS, shows activity-dependent plasticity—that inputs from the periphery or from the brain can cause lasting changes in the spinal cord that affect its output far into the future. The spinal cord possesses capacities for neuronal and synaptic plasticity comparable to those found elsewhere in the CNS.

In spite of the substantial evidence for activity-dependent plasticity in the spinal cord, its role in the acquisition and maintenance of behaviors in normal states and in the aftermath of CNS injury has only recently begun to be properly recognized and explored. This new interest and effort derive largely from two factors. The first is the remarkable excitement and energy now focused on developing new treatments for spinal cord injury (Bregman et al 1997, Fawcett 1998, Amar & Levy 1999, Tuszynski & Kordower 1999). The newly recognized possibilities for CNS regeneration inevitably raise the issue of how regenerated neuronal tissue is to become useful, of how it will come to provide normal, or at least acceptable, function. A normally functioning adult spinal cord is a product of appropriate activity-dependent plasticity during early development and throughout subsequent life. Thus, a newly regenerated spinal cord will probably not be properly or even acceptably configured for effective use (Muir & Steeves 1997). It is likely to display diffuse infantile reflexes or other disordered and dysfunctional outputs. As methods for inducing spinal cord regeneration develop, methods for redeveloping spinal cord function—for re-educating the newly regenerated spinal cord—will become essential. This anticipated need compels attention to activity-dependent spinal cord plasticity, to the processes by which spinal cord neurons and synapses are shaped to serve important functions as diverse as locomotion, urination, and playing a musical instrument. Furthermore, recent appreciation of the latent capacities for plasticity of the injured unregenerated spinal cord provides additional incentive for exploring activity-dependent plasticity in the spinal cord. Understanding this plasticity is essential for understanding both the changes that occur after injury and the processes that can be accessed and guided to restore useful function.

The second factor is the growing recognition, driven by data from a variety of laboratory models, that the acquisition and maintenance of both normal motor

performances and the abnormal behaviors associated with disease involve activity-dependent plasticity at multiple sites throughout the CNS, including the spinal cord. The peripheral and descending inputs that occur during practice or as a result of trauma or disease change the spinal cord, and these changes combine with changes elsewhere in the CNS to change behavior. Thus, knowledge of the mechanisms of spinal cord plasticity and its interactions with activity-dependent plasticity elsewhere in the CNS is important for understanding normal behaviors, as well as for understanding the complex disabilities produced by disorders such as spinal cord injury.

The Present Review

The focus of this review is activity-dependent spinal cord plasticity (that is, lasting change in spinal cord function produced by peripheral and/or descending inputs) and its impact on motor function in health and disease. Other kinds of spinal cord plasticity—such as the long-term effects of neurotrophins or the processes triggered by axotomy (e.g. Mendell 1988, 1999; Wilson & Kitchener 1996; Chen & Frank 1999)—are not addressed. The primary intent is to review the range of clinical and laboratory phenomena that reflect or elucidate activity-dependent spinal cord plasticity, with particular attention to its role in normal and abnormal behaviors.

The first section addresses plasticity induced by sensory input in spinal cord that has been isolated from descending influence. Activity-dependent plasticity in this setting provides insight into neuronal and synaptic mechanisms and has great relevance for the treatment of spinal cord injury. The following section addresses spinal cord plasticity that occurs in the intact CNS and often involves both sensory input from the periphery and descending input from the brain. This is the setting in which spinal cord plasticity usually occurs and is most relevant to motor function in health and disease. The final section addresses the relationships between activity-dependent plasticity and behavioral change. Activity-dependent plasticity at multiple spinal and supraspinal sites underlies the acquisition and maintenance of both normal and abnormal behaviors, and the relative simplicity and accessibility of the spinal cord facilitates recognition and exploration of this complex plasticity. Furthermore, the necessity for and inevitability of this complex plasticity suggest principles that should guide development of new therapeutic methods for promoting recovery of function after spinal cord injury.

PLASTICITY PRODUCED BY SENSORY INPUT IN THE ISOLATED SPINAL CORD

The isolated spinal cord, deprived of descending influence from the brain, has been a popular and productive experimental model for more than a century, providing, by virtue of its accessibility and relative simplicity, a large part of present-day

understanding of CNS neuronal and synaptic function. Many studies have explored the persistent effects of sensory input. While most have studied the relatively short-term effects (i.e. minutes to hours) of single inputs or simple combinations of inputs, more recent studies have investigated the long-term effects (i.e. weeks to months) of complex sequences of sensory input and are directly related to treatment of spinal cord injury.

In this work the primary measures of spinal cord function have been the two most prominent classes of short-latency spinal cord responses to peripheral inputs: flexion withdrawal reflexes and proprioceptive reflexes (Matthews 1972, Baldissera et al 1981, Burke 1998, Kandel et al 2000). Flexion withdrawal reflexes are mediated by oligosynaptic pathways to spinal motoneurons from unmyelinated C nociceptive fibers and from small myelinated A-delta fibers that are also activated by noxious stimuli. They are normally limited to those muscles that withdraw the body from the painful stimuli. After spinal cord injury or with other disorders, they may become diffuse and hyperactive and thereby contribute to spasms and postural abnormalities. Proprioceptive reflexes are mediated by mono- and oligosynaptic pathways to spinal motoneurons from larger afferents that innervate muscle spindles, Golgi tendon organs, and other receptors that reflect muscle length and tension and limb position. The simplest proprioceptive reflex is the spinal stretch reflex (SSR), or tendon jerk, which is mediated largely by a monosynaptic pathway made up of the Ia afferent fiber from the muscle spindle, its synapse on the motoneuron, and the motoneuron. It produces contraction in response to sudden muscle stretch, and descending activity affects its gain through several mechanisms. Other proprioceptive reflexes, both excitatory and inhibitory, reflect more complex segmental responses to muscle length and tension and limb position, and are also regulated by descending activity.

Simple Sensory Inputs

Flexion withdrawal reflexes in the isolated spinal cord display habituation and sensitization with a variety of protocols (Mendell 1984). Most research has been oriented toward clarifying pain mechanisms and has focused on sensitization of spinal cord responses to C-fiber input. This work is the subject of numerous recent reviews (Pockett 1995, Randić 1996, Baranauskas & Nistri 1998, Alvares & Fitzgerald 1999, Woolf & Costigan 1999, Yaksh et al 1999, Dubner & Gold 1999, Herrero et al 2000) and is only briefly summarized here.

In the most thoroughly studied phenomenon, usually referred to as wind-up, (Mendell & Wall 1965), repetitive C-fiber stimulation at rates >0.3 Hz leads to progressive increase in the neuronal excitation produced by each stimulus. Short series of stimuli (e.g. 30 in 30 sec) produce sensitization lasting minutes, and longer series can produce sensitization lasting much longer. Wind-up is not limited to the dorsal horn neurons directly contacted by C fibers; other spinal cord neurons, including motoneurons in ventral horn, may also exhibit it. The underlying mechanisms vary across species, neuronal populations, and protocols, and

multiple processes probably contribute in individual instances. Initially, release of the excitatory amino acids glutamate and aspartate and tachykinins such as substance P activates NMDA receptors leading to calcium entry and activates second messenger systems that affect proteins controlling membrane excitability. Eventually, activation of c-fos and other early immediate genes may take place, and expansion of the receptive fields of dorsal horn neurons and phenotypic conversion of A-beta fibers to C-fiber-like behavior can occur. As illustrated in Figure 1*A*, high-frequency stimulation can produce persistent increases in neuronal excitability comparable to long-term potentiation elsewhere in the CNS. The spinal cord plasticity induced by C-fiber input contributes to the clinical syndromes of spontaneous pain, abnormal sensitivity to noxious stimuli, or even innocuous stimuli, and referred pain that often follow injury to peripheral tissues.

While most evidence for spinal cord plasticity produced by afferent input relates to C-fiber stimulation, activity in other afferent populations has been linked to change in the spinal cord. Brief periods of high-frequency stimulation of the largest sensory fibers, Ia afferents from muscle spindles, produce posttetanic potentiation lasting seconds to minutes, and longer periods of stimulation can produce potentiation lasting hours (Lloyd 1949, Kandel 1977).

Over the past 70 years, associative conditioning phenomena, both classical and operant, have been repeatedly demonstrated in the spinal cords of cats, dogs, and rats (reviewed in Patterson 1976, Kandel 1977, Thompson 2001). These models normally use stimuli that generate C-fiber input. In a well-characterized classical conditioning protocol in the isolated lumbosacral spinal cord of decerebrate cats, Durkovic and colleagues used superficial peroneal nerve stimulation as the unconditioned stimulus (US), saphenous nerve stimulation as the conditioned stimulus (CS), and tibialis anterior muscle contraction as the response (Durkovic 1985, 1986). As illustrated in Figure 1*B*, paired presentation of the stimuli, with the CS preceding the US by one second, quickly produced a substantial increase in the response to the CS alone, while unpaired presentation led only to a decrease in the response to the CS alone. The phenomenon exhibited the features of classical conditioning, including characteristic dependence on the delay between CS and US. The spinal cord plasticity underlying this conditioning appears to involve interneurons conveying the sensory input, rather than the sensory afferents or the motoneurons themselves.

Training Regimens

Locomotion The rhythmical and sequential activation of muscles that underlies locomotion is a characteristic function of the vertebrate CNS, and one in which the spinal cord plays a central role (Rossignol 1996, Kiehn et al 1998, Orlovsky et al 1999). Locomotion, whether swimming, flying, or walking, is produced by interconnected spinal neurons that together constitute a locomotor pattern generator (LPG). The spinal LPG is activated by supraspinal influences that descend from locomotor regions in the brainstem and thalamus, and its operation is

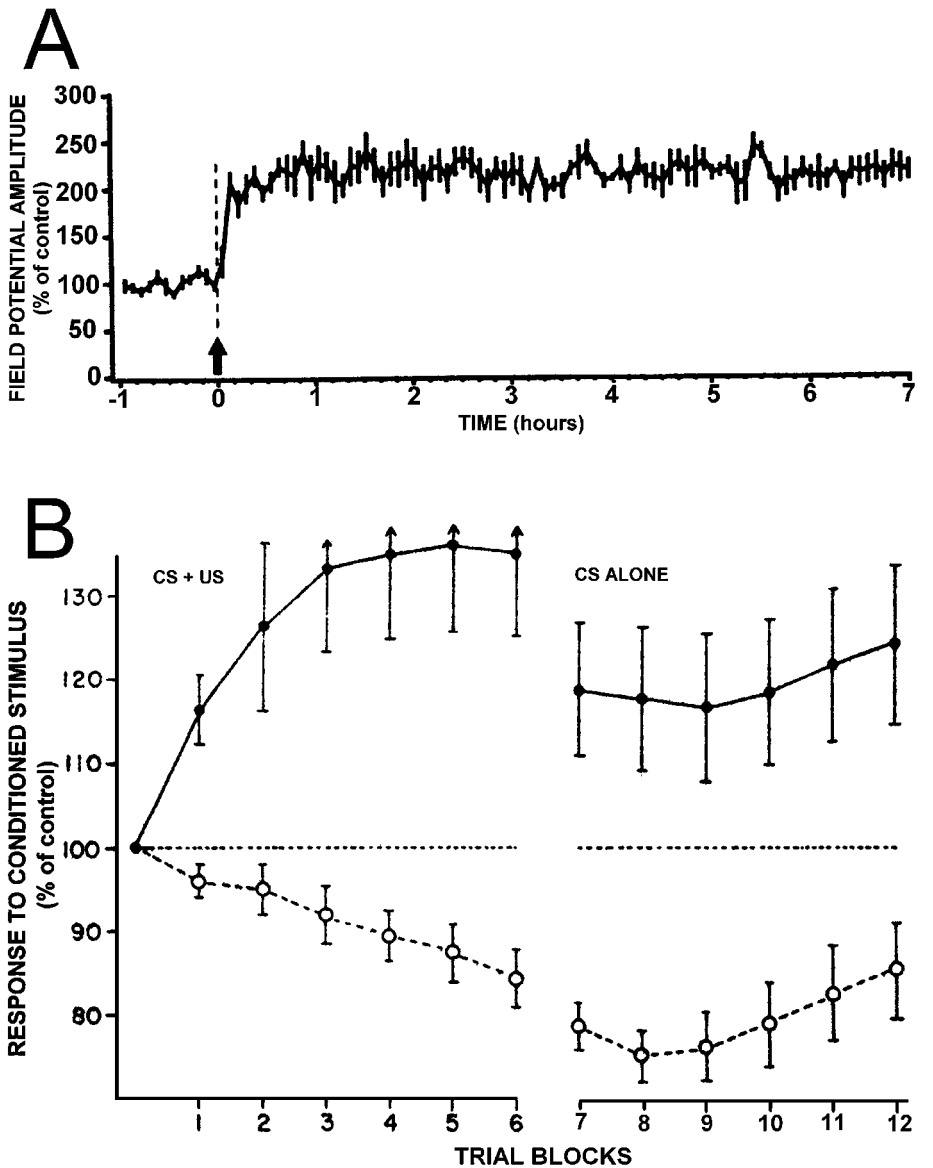


Figure 1 Activity-dependent plasticity induced by sensory input in the isolated spinal cord. (*A*) Long-term potentiation of field potentials evoked by stimulation (*arrow*) of C fibers in rat sciatic nerve. Modified from Liu & Sandkühler (1997). (*B*) Classical conditioning in the cat. Paired presentation (*solid line*) of the conditioned stimulus (CS) and unconditioned stimulus (US) for six blocks of five trials each increases the response to the CS from its control level, while unpaired presentation (*dashed line*) produces only habituation to the CS. The increased response to the CS is still evident with subsequent presentation of the CS alone. Modified from Durkovic (1985).

continually adjusted and refined by proprioceptive and cutaneous inputs from the periphery. The existence and importance of the spinal LPG is most apparent in lower vertebrates such as the lamprey or chick, in which robust locomotion is evident after removal of all supraspinal influence. Its existence is also evident in higher vertebrates such as the cat, in which the lumbosacral spinal cord is quite capable of producing well-coordinated treadmill locomotion after transection of the thoracic spinal cord has removed supraspinal control. Furthermore, studies in people with spinal cord injuries suggest the existence of an LPG in the human lumbrosacral spinal cord (Holmes 1915, Kuhn 1950, Bussel et al 1988, Calancie et al 1994, Dietz et al 1995, Dobkin et al 1995, Dimitrijevic et al 1998, Rossignol 2000). If the operation of a human LPG could be encouraged and guided—by training programs, pharmacological agents, sensory stimulation, surviving descending pathways, or other means—useful locomotion might be restored. In the work motivated by this possibility, impressive new evidence for activity-dependent plasticity in the spinal cord has emerged.

Fifty years ago, Shurrager & Dykman (1951) reported that treadmill walking in spinalized cats (i.e. cats with transected spinal cords) improved with training. Over the past 15 years several energetic research groups have confirmed this phenomenon in spinalized animals and in humans with spinal cord injuries, described its major features, and begun to reveal its mechanisms and define its potential role in therapy (Lovely et al 1986, Barbeau & Rossignol 1987, Barbeau et al 1999). In the typical protocol, cats were subjected to complete spinal cord transection at a thoracic level and then began a regimen in which they were trained for 30–60 min per day to walk on a treadmill with their hindlimbs while their forelimbs stood on a platform. Early in training, coordinated locomotion occurred only when the experimenter provided weight support for the hindquarters and a strong nonspecific sensory input such as stimulation of the perineum or tail. The primary observation was that coordinated locomotion developed and improved over days and weeks. Animals gradually walked faster, with longer steps, and for longer periods, and eventually required little or no weight support or sensory stimulation to do so. Careful electromyographic and kinematic analyses described this locomotion in detail (Bélanger et al 1996). While subtle differences from normal were found, spinal locomotion after training was in major respects comparable to that found prior to injury.

Locomotion was much better in cats exposed to treadmill training than in cats that received only normal nursing care after injury (de Leon et al 1998a). Although untrained animals regained some locomotor ability, they were clearly inferior to trained animals. Figure 2*A* illustrates the marked difference. The noradrenergic alpha-2 agonist clonidine facilitated early training, reducing the need for sensory stimulation and speeding improvement (Chau et al 1998). The improved locomotion produced by training persisted when training stopped, declining very little over 6 weeks, and only showing significant loss at 12 weeks (de Leon et al 1999a).

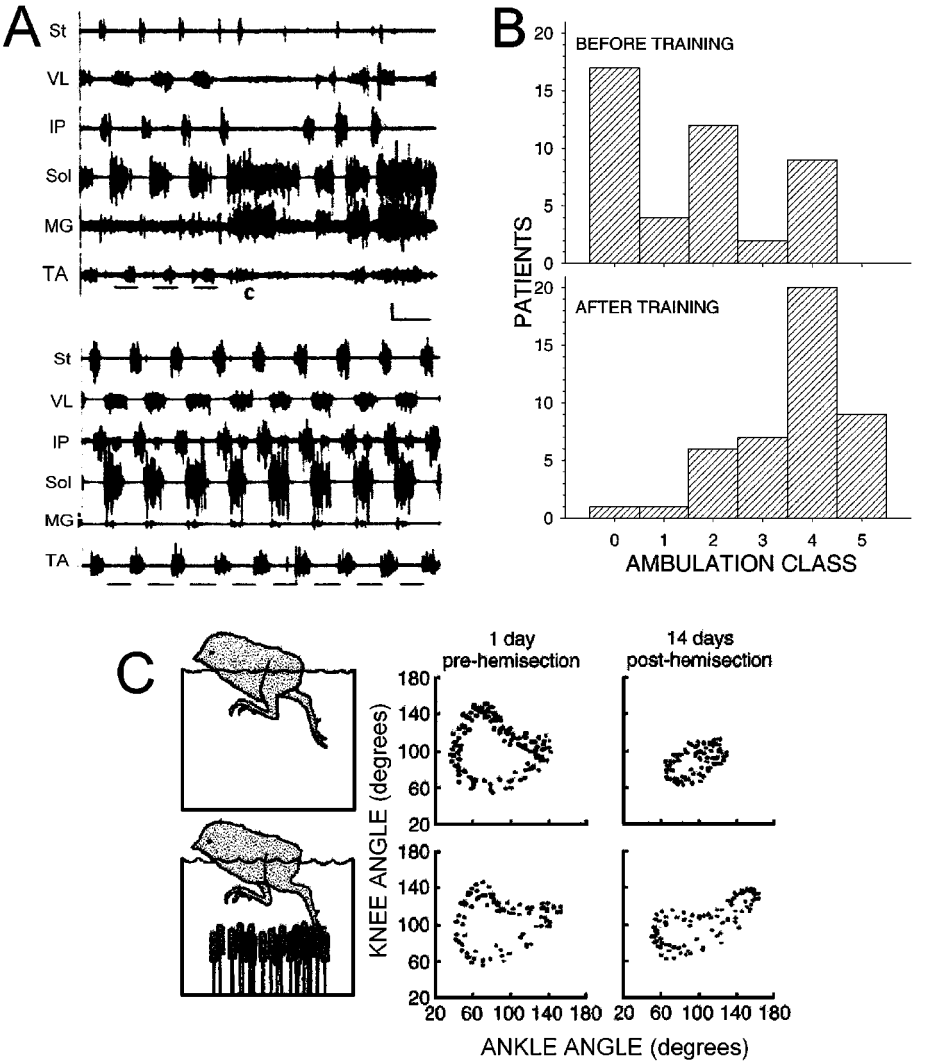
Functional improvement was found to depend quite specifically on the nature of the training regimen. A regimen in which cats were trained to stand rather than

to walk clearly improved standing (de Leon et al 1998b). If stand training was confined to one leg, improvement was focused in that leg. Furthermore, animals trained to stand did not walk well on the treadmill, and animals trained to walk did not stand well. Nevertheless, animals trained to perform one task could then be trained to perform the other. In addition, locomotor deficits produced by muscle denervation abated with continued training (Bouyer et al 2001). Furthermore, studies of motor unit properties after spinal cord transection and with or without training, indicated that the training-induced improvements in walking and standing were not attributable to peripheral changes in muscle strength or other motor unit properties (Roy & Acosta 1986; Roy et al 1991, 1998). They appeared to be largely or wholly due to activity-dependent spinal cord plasticity.

Comparable treadmill training is being evaluated in humans with complete or incomplete spinal cord injuries (Barbeau & Fung 1992; Harkema et al 1997; Wernig et al 1995, 1998; Dietz et al 1995; Dobkin 1998; Field-Fote 2000). In people who retain some control of leg muscles, treadmill training assisted by weight-support (with a harness or other device) can improve locomotion, producing greater speed, strength, coordination, and endurance, and reduce need for assistive devices (e.g. Figure 2*B*). Comparison of spinal cord–injured patients who underwent treadmill training with others who simply received conventional rehabilitation indicates that treadmill training increases walking ability. Improvement has been reported both in patients recently injured and in those injured a long time ago, and can persist beyond the cessation of formal training. The encouraging initial studies await confirmation by randomized clinical trials (Dobkin 1999).

The spinal cord plasticity that underlies training-induced functional improvement clearly depends on the pattern of afferent, efferent, and interneuronal activity that occurs during training. Recent work provides some insight into crucial aspects of that activity. A certain minimum level of appropriately timed sensory input appears to be essential (Rossignol & Bouyer 2001). The importance of sensory input is evident in chicks with spinal cord hemisection, in which training to walk is much more effective than training to swim, even though the behaviors are very similar (Muir & Steeves 1995, Muir 1999). The difference is attributable to the greater phasic sensory input that occurs during walking—the input produced by foot contact and the excitation of cutaneous and proprioceptive receptors associated with it. When comparable sensory input was provided during swim training, performance improved markedly, as illustrated in Figure 2*C*. Functional electrical stimulation, both sensory and motor, can also contribute to spinal cord plasticity and peripheral change, and can thereby improve performance (Peckham & Creasey 1992, Muir & Steeves 1997, Stein 1999).

The performance improvements produced by treadmill training in cats appear to be associated with change in glycinergic inhibition in the spinal cord. The effects of the glycinergic inhibitor, strychnine, were evaluated in cats that had been trained over 12 weeks to either walk or stand (de Leon et al 1999b). In cats trained to walk locomotion proceeded as before. In contrast, in cats trained to stand locomotion was much improved when strychnine reduced glycinergic inhibition. Furthermore,



when cats trained first to walk were subsequently trained to stand, so that walking performance deteriorated, strychnine restored walking. Conversely, if cats first trained to stand were subsequently trained to walk, strychnine then had no effect on their walking. These results suggest that locomotor training reduces the level of glycinergic inhibition in the spinal cord.

Urination and Other Essential Functions Although the effects of spinal cord injury on locomotion and other voluntary limb movements usually receive the most attention and have been the focus of most research, its devastating effects on urinary tract, bowel, and sexual function, and on blood pressure and body temperature control, are of equal or greater concern to those affected (as well as to their families and caregivers) and can have greater impact on their lives (Ronthal 1998, Biering-Sørensen et al 1999, McKinley et al 1999, Teasell et al 2000, Chen & Nussbaum 2000, Linsenmeyer 2000, Monga et al 1999, Stiens et al 1997, Weld & Dmochowski 2000). Satisfactory urinary tract function is particularly critical to the survival and well-being of people with spinal cord injuries. Urinary tract infections and eventual kidney failure contributed greatly to the dismal prognosis of spinal cord injury prior to the early twentieth century, and appropriate bladder management is an essential feature of current rehabilitation and long-term care protocols.

Normal urinary tract function depends on appropriate reciprocal relationships between activation of bladder muscle and activation of the urethral sphincter muscles (de Groat et al 1997, Yoshimura 1999). During urine accumulation, bladder muscle is relatively inactive and sphincter muscles are tonically active. Urination is triggered by stretch receptors in the bladder wall and executed by spinal and supraspinal reflex pathways that excite bladder muscles and relax sphincter muscles. After transection of the cervical or thoracic spinal cord, and after the

Figure 2 Effects of locomotor training of the isolated spinal cord. (*A*) Electromyographic activity on the treadmill in spinalized cats that have (*bottom traces*) or have not (*top traces*) undergone treadmill training. Consistent rhythmical muscle activation and consistent walking (shown by the *horizontal lines* indicating each stance phase) are present only in the trained cat. Rhythmical muscle activation and walking are imperfect and sporadic in the untrained cat. (C, collapse; St, semitendinosus; VL, vastus lateralis; IP, iliopsoas; Sol, soleus; MG, medial gastrocnemius; TA, tibialis anterior.) Scale: 1 sec and 1.0 mV (2.0 for Sol). Modified from de Leon et al (1998a). (*B*) Ambulation performance before and after treadmill training in humans with spinal cord injuries. Those in classes 0–2 are wheelchair-bound, those in class 5 can walk >5 steps without any assistive device. Ambulation is greatly improved after training. Modified from Wernig et al (1995). (*C*) Knee and ankle excursions during swimming in normal chicks and in the same chicks after spinal cord hemisection followed by 14 days of swim training with (*bottom*) or without (*top*) plantar stimulation during the phase of movement equivalent to the stance phase of walking. After training movement is closer to normal in hemisected chicks that have received planter stimulation. Modified from Muir (1999).

acute period of spinal shock and reflex depression, urination is more frequent and less effective, owing to changes in sensory afferents from the bladder and in spinal cord reflex pathways that receive this afferent input. C fibers innervating the bladder wall, which normally convey nociceptive information and have relatively high firing thresholds, undergo histological and chemical changes that lower their thresholds and make them the primary trigger for urination. Their change in threshold is thought to result from change in sodium and potassium channels, due at least in part to increases in trophic factors such as nerve growth factor (NGF) caused by chronic bladder distension. The contribution of altered afferent activity itself to spinal cord plasticity remains unclear, but the demonstrated effects of altered C-fiber input in other situations (see above) suggest that it also has a role here. Chronic spinal cord injury also produces loss of the coordinated sphincter relaxation that normally accompanies bladder contraction and urination. Spasmodic sphincter contractions interfere with urine flow and lead to incomplete emptying and bladder distension. The abnormalities in spinal pathway function that account for this loss of coordination remain undefined, and the extent to which they reflect plasticity produced by the known changes in afferent input and afferent neurons and by the loss of supraspinal reflex pathways remains to be determined.

Activity-dependent spinal cord plasticity probably contributes to the disordered urinary tract function after spinal cord injury and seems likely to also contribute to the abnormalities in other functions, such as bowel control and blood pressure regulation. Functional electrical stimulation to elicit voiding in those with spinal cord injuries is in clinical use (Brindley 1995, Rijkhoff et al 1997, Van Kerrebroeck 1998), and a preliminary effort to classically condition urination after spinal cord injury showed temporary success (Ince et al 1978). Concerted efforts to induce and guide activity-dependent plasticity to improve these functions after spinal cord injury, efforts comparable to those now focused on restoring locomotion, are likely to yield important new therapeutic advances.

PLASTICITY PRODUCED BY DESCENDING INPUT AND ASSOCIATED PERIPHERAL INPUT

Descending inputs to the spinal cord are a continual barrage of activity in a variety of pathways. The immediate short-term products of this activity—voluntary movements, responses to peripheral disturbances, activation of the spinal cord circuitry underlying locomotion, respiration, and urination, task-specific adjustments in spinal reflex pathways—are readily apparent and have received much attention. The immediate effects of loss or distortion of descending activity due to supraspinal or spinal trauma are similarly apparent. In contrast, the long-term effects of descending input on the spinal cord are not so obvious and have received less attention. Nevertheless, while the rapid effects of descending input are easy to see and convenient to study, the gradual effects are also important. They help establish and maintain spinal cord function in a state most amenable to

effective performance. Activity-dependent plasticity, driven by descending input and associated peripheral input, shapes spinal cord function during development and continues to modify it throughout life.

Abnormal Descending Input

The immediate effects of spinal cord contusion or transection—loss of purposeful movement and sensation and profound suppression of spinal reflexes below the level of the lesion—have been known throughout history and are described in the oldest medical records (Ronthal 1998). Prior to the twentieth century, however, the long-term effects were largely unknown, because most victims succumbed rapidly to respiratory or urinary tract infections or to other consequences of immobility and autonomic dysfunction. The wars of the past century spurred development of comprehensive programs for acute and chronic management of the numerous problems attendant on spinal cord injury. As a result, most people with severe spinal cord injuries can now have nearly normal life spans, and the long-term effects of these injuries are extremely significant.

Destruction or severe impairment of spinal cord pathways initiates a sequence of changes in spinal cord function below the lesion that develops over days, weeks, and months (Riddoch 1917, Kuhn 1950, Mountcastle 1980, Ronthal 1998, Hiersemenzel et al 2000). At first, function is severely depressed and reflexes are difficult or impossible to elicit. This period of spinal shock abates over several weeks in humans. Then, over a longer period, the reflexes become abnormally strong. This is commonly manifested by increased resistance to passive muscle stretch, particularly in antigravity muscles (i.e. leg extensors and arm flexors), hyperactive tendon jerks, and increased flexion withdrawal responses to painful stimulation. These signs comprise the syndrome of spasticity and are accompanied by changes in a variety of electrophysiological measurements. The gradual development of these effects reflects spinal cord plasticity caused by the destruction of supraspinal connections, by the accompanying loss of descending input, and by associated changes in peripheral input.

Physiological studies give some insight into the mechanisms underlying this long-term plasticity. After cord transection in cats, Ia afferent excitatory postsynaptic potentials (EPSPs) in triceps surae motoneurons are larger than normal and have faster rise times, the motoneurons have more positive firing thresholds and shorter afterhyperpolarizations, and changes occur in motor unit properties and type distributions (Nelson & Mendell 1979, Cope et al 1986, Munson et al 1986, Hochman & McCrea 1994a–c). These effects differ across muscles. In both humans and animals spinal interneuronal pathways also change after spinal cord transection or injury (Boorman et al 1991, Thompson et al 1992, Shefner et al 1992). For example, both recurrent inhibition, mediated by the Renshaw cell, and reciprocal inhibition, mediated by the Ia inhibitory interneuron, appear to be increased. Electron microscopic analysis of motoneuron synaptic coverage after spinal cord injury reveals changes in specific terminal populations (Tai & Goshgarian 1996, Tai et al 1997).

These clinical and laboratory data demonstrate that spinal cord injury changes the distal spinal cord. However, they do not distinguish plasticity due to the change in descending input from plasticity due to pathway destruction and the accompanying retrograde and anterograde effects, or from plasticity due to accompanying peripheral changes. Spinal cord plasticity clearly attributable to a more limited and specific change in descending input was first demonstrated in the 1920s, when Anna DiGiorgio altered descending input to the spinal cord by lesioning one side of the cerebellum in anesthetized dogs, rabbits, and guinea pigs (DiGiorgio 1929, 1942). The immediate response was an asymmetric hindlimb posture: One leg was flexed and the other was extended. After a variable delay she removed the descending input responsible for this asymmetry by cutting the thoracic spinal cord. When the delay was short transection eliminated the asymmetric posture. However, when the delay was longer the asymmetric posture survived transection. It persisted even though all descending input was gone. Subsequent experiments in a variety of species confirmed her results and showed that they were not due to peripheral mediation, such as change in sensory receptor function (Manni 1950, Gerard 1961). In the 1960s Ralph Gerard and his colleagues defined in rats the time course of the development of asymmetry that survived transection (Chamberlain et al 1963). Persistent asymmetry did not occur if the delay between cerebellar lesion and spinal cord transection was only 30 min, and rose rapidly to its maximum value as the delay increased to one hour. The authors concluded that a period of 45 min was needed to establish significant persistent asymmetry. This phenomenon was considered by Gerard and others to be a good model for the fixation or consolidation of memory believed to occur at higher levels of the CNS, and was therefore called spinal fixation. Comparable phenomena occur in the spinal cord with a variety of supraspinal lesions and can also follow manipulation of labyrinthian sensory inputs (Giulio 1952, Straka & Dieringer 1995). Clearly, altered descending input that lasts for sufficient time produces spinal cord plasticity that persists after the input stops.

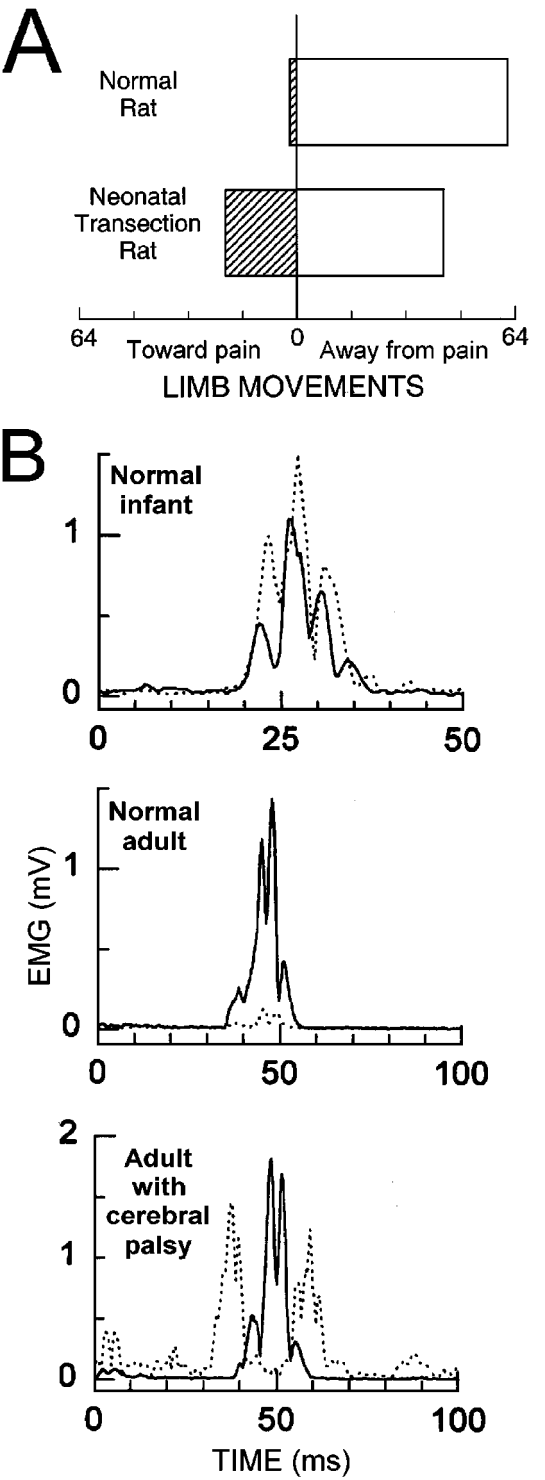
Descending Input in Normal Life

Spinal cord plasticity produced by long-term changes in descending activity is not limited to abnormal or pathological situations. It appears to be a feature of normal life, both during development and during later life as well. The acquisition of motor skills, both standard skills such as walking and writing and specialized skills such as dancing and piano playing, are acquired only through prolonged practice, which involves specific patterns of activity in descending pathways and associated patterns of activity in sensory afferents. The continued maintenance of these skills, in spite of peripheral and central changes associated with growth and aging, is also likely to involve prolonged adjustments in descending inputs. Diverse evidence indicates that spinal cord plasticity caused by descending activity contributes to motor development in childhood and to the learning of motor skills later in life.

Shaping of Spinal Cord Reflexes During Development Descending input during the first years of life gradually modifies spinal reflexes and helps produce the normal adult reflex pattern. Both flexion withdrawal reflexes and muscle stretch reflexes are shaped by this influence. Schouenborg and colleagues have demonstrated the importance of descending influence in producing adult flexion withdrawal reflexes (Levinsson et al 1999). In the normal neonatal rat focal nociceptive stimulation produces diffuse and often inappropriate muscle contractions and limb movements. In contrast, in the normal adult such stimulation excites the appropriate muscles, that is, the muscles that withdraw the limb from the painful stimulus. As Figure 3*A* illustrates, neonatal spinal cord transection prevents development of the adult pattern, so that nonspecific and inappropriate flexion withdrawal reflexes remain in the adult.

The importance of descending input during early life in shaping the spinal cord circuitry that produces muscle stretch reflexes is shown by the effects of the perinatal supraspinal lesions associated with cerebral palsy. In normal infants muscle stretch produces very short-latency spinally mediated stretch reflexes in both the stretched muscles and their antagonists (Myklebust et al 1986, O'Sullivan et al 1991). Normally, the antagonist stretch reflexes gradually disappear during childhood, leaving the adult with standard, so called knee-jerk, reflexes, limited to the stretched muscles. However, in infants in whom supraspinal damage distorts activity in descending pathways, this normal evolution often fails to occur, so that antagonist stretch reflexes last into adulthood and contribute to motor disability. Figure 3*B* shows agonist and antagonist stretch reflexes from normal infants and normal adults, and from adults with cerebral palsy. In affected individuals, the original damage is supraspinal. Thus, the likely explanation for the abnormal persistence of infantile spinal reflexes into adulthood is the absence or distortion of the long-term descending input that normally eliminates or suppresses these reflexes over the course of development. The development of adult reflex patterns presumably reflects activity-dependent plasticity produced by appropriate descending input and by the appropriate patterns of peripheral input that the descending input produces by influencing muscle activation and limb movement.

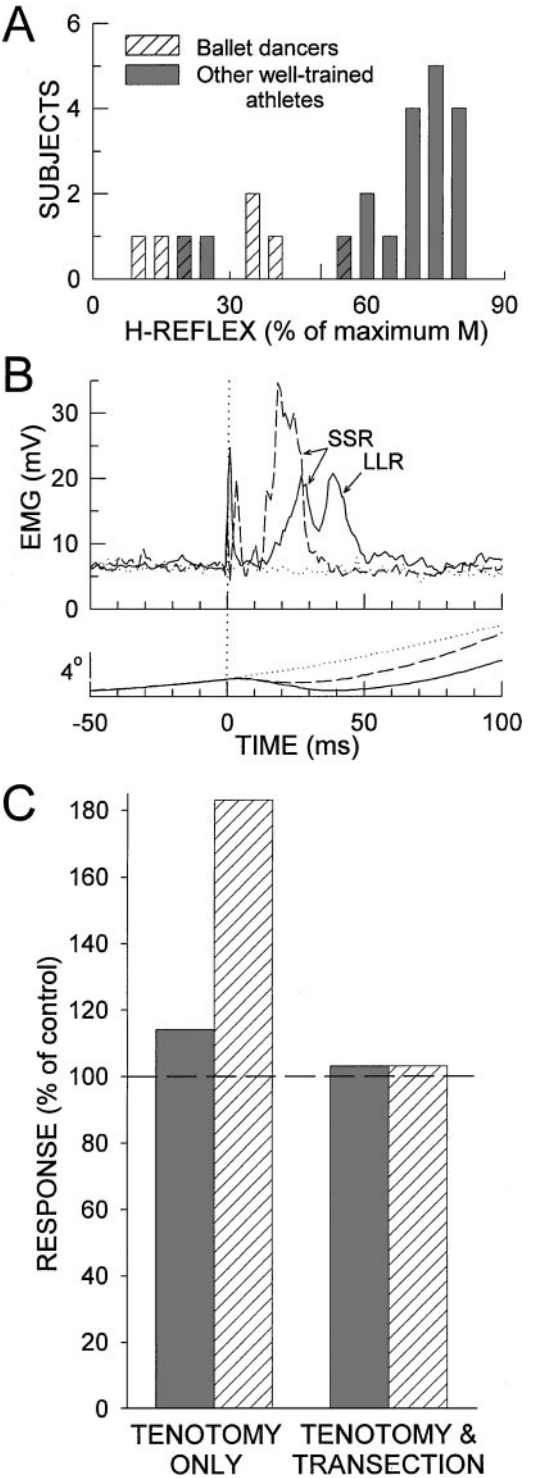
Acquisition and Maintenance of Motor Skills The acquisition of motor skills later in life is associated with less dramatic changes in spinal cord circuitry. In adults spinal reflexes correlate with the nature, intensity, and duration of motor training. The strengths of spinal reflexes depend on past physical activity and training (Rochcongar et al 1979, Goode & Van Hoven 1982, Casabona et al 1990, Koceja et al 1991, Nielsen et al 1993). The most frequently studied reflexes have been the spinal stretch reflex (SSR) (produced mainly by a monosynaptic pathway consisting of the Ia afferent from the muscle spindle, its synapse on the motoneuron, and the motoneuron itself), and its electrical analog, the H-reflex, which is elicited by direct electrical stimulation of the Ia afferents (Magladery et al 1951, Matthews 1972, Henneman & Mendell 1981, Brown 1984).



These reflexes differ between athletes and nonathletes and between different groups of athletes. A particularly valuable study reported H-reflexes in soleus muscles of people who were either sedentary, moderately active, or extremely active, or were professional ballet dancers (Nielsen et al 1993). Both the H-reflex and disynaptic reciprocal inhibition were larger in moderately active subjects than in sedentary subjects, and even larger in extremely active subjects. Because the human soleus muscle consists almost entirely of slow (i.e. type I) fibers, exercise-induced change in motor unit properties cannot readily account for the reflex increase seen with activity. Furthermore, the most remarkable finding, illustrated in Figure 4*A*, was that both the H-reflex and disynaptic reciprocal inhibition were lowest in the dancers, even though they were much more active than any other group. Their values were lower than those of sedentary subjects and much lower than those of active subjects. Noting that muscle cocontraction is accompanied by increased presynaptic inhibition and decreased reciprocal inhibition, the authors speculated that the prolonged cocontractions required by the classical ballet postures lead to persistent decreases in synaptic transmission at the Ia synapses, and thereby account for the reductions in H-reflexes and reciprocal inhibition. Viewed from the perspective of performance, the decreased direct peripheral influence on motoneurons indicated by the smaller reflexes may increase cortical control and allow more precise movement.

Laboratory evidence for training-induced spinal cord plasticity comes from a study in which monkeys were trained to make smooth repetitive flexion and extension movements at the elbow, and random brief perturbations were superimposed (Meyer-Lohmann et al 1986). Over months and years, the SSR elicited by the perturbation gradually increased so that it took over the task of responding to the torque pulse, while later reflex responses gradually disappeared. As illustrated in Figure 4*B*, the larger SSR was adaptive: it was associated with more rapid and effective correction of the change in position caused by the perturbation. The

Figure 3 Activity-dependent plasticity produced by descending input during development. (*A*) Direction of limb movement produced by flexion withdrawal responses to a nociceptive stimulus in normal adult rats and in adult rats subjected to spinal cord transection just after birth. Direction is almost always appropriate, i.e. away from the stimulus in normal adults, but is often inappropriate in transected adults. Neonatal transection prevents normal shaping of flexion withdrawal reflexes by descending input. Modified from Levinsson et al (1999). (*B*) Short-latency electromyographic 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 occur in both muscles. In a normal adult a reflex occurs only in the stretched muscle, i.e. the soleus. Little or no response occurs in the tibialis anterior. In contrast, in an adult with cerebral palsy, in whom perinatal supraspinal injury has impaired the descending input responsible for development of normal adult reflexes, the infantile pattern persists: Reflexes occur in both muscles. From B Myklebust, unpublished data (see Myklebust et al 1982, 1986 for comparable data).



investigators concluded that the results "demonstrate a long-term functional plasticity of the sensorimotor system of adult animals and suggest a growing role for fast segmental mechanisms in the reaction to external disturbances as motor learning progresses" (p. 398).

Additional evidence for adaptive spinal cord plasticity during life and in response to specific demands comes from studies of reflex changes in humans associated with aging, space flight, and specialized training paradigms, and studies of reflex changes in animals associated with chronic alterations in peripheral input produced by tenotomy (Figure 4*C*) or by application of tetrodotoxin to the peripheral nerve (Beránek & Hnik 1959, Kozak & Westerman 1961, Robbins & Nelson 1970, Goldfarb & Muller 1971, Gallego et al 1979, Sabbahi & Sedgwick 1982, DeVries et al 1985, Reschke et al 1986, Webb & Cope 1992, Trimble & Koceja 1994, Angulo-Kinzler et al 1998, Yamanaka et al 1999, Zheng et al 2000).

All these data suggest that gradual activity-dependent changes in spinal cord function contribute to the acquisition and maintenance of motor skills throughout life. Their prolonged time course and dependence on repetition probably account in part for the lengthy periods and intensive practice required for acquisition and maintenance of athletic skills and other motor skills such as playing a musical instrument. At the same time, while experiments of the DiGiorgio type demonstrate that abnormal descending input can modify the spinal cord, the spinal reflex changes described in this section might conceivably be imposed by concurrent descending activity and/or might reflect peripheral changes: The spinal cord itself might have undergone no intrinsic or enduring change. Thus, these data strongly suggest, but do not demonstrate, that normal descending inputs produce spinal cord

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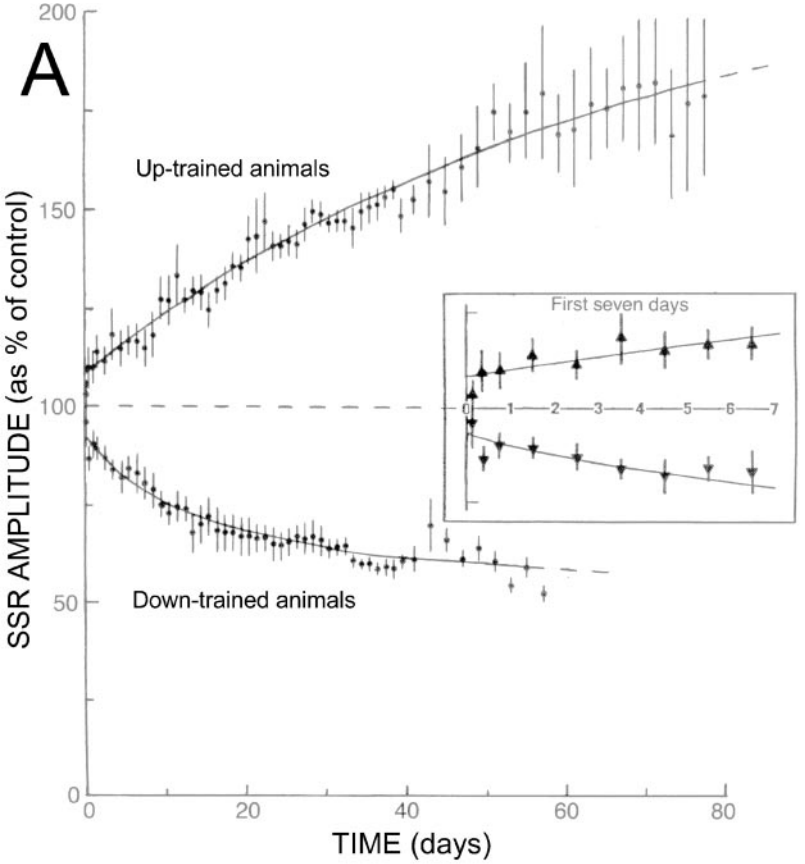
Figure 4 Activity-dependent spinal cord plasticity produced by descending input occurring during skill acquisition or in response to a peripheral lesion. (*A*) Soleus H reflexes are much smaller in professional ballet dancers than in other well-trained athletes (e.g. runners, swimmers, cyclists). (H-reflexes of sedentary subjects fall in between.) Modified from Nielsen et al (1993). (*B*) Working for reward, monkeys performed an elbow flexion-extension task on which brief perturbations were randomly superimposed. Biceps electromyographic activity and elbow angle (flexion is 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 produces 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 has disappeared. The SSR has gradually taken over the role of opposing the perturbation. This improves performance: The perturbation of the smooth course of elbow flexion is smaller and briefer. Modified from Meyer-Lohmann et al (1986). (*C*) Tenotomy in cats increases the monosynaptic ventral root response to stimulation of the nerve from a tenotomized muscle (*hatched*) after 1–4 weeks. The response to stimulation of the nerve from a nontenotomized muscle (*solid*) does not change. The increase does not occur in cats in which the spinal cord was transected just prior to tenotomy. Thus, descending input in response to tenotomy appears to induce the spinal cord plasticity. Modified from Kozak & Westerman (1961).

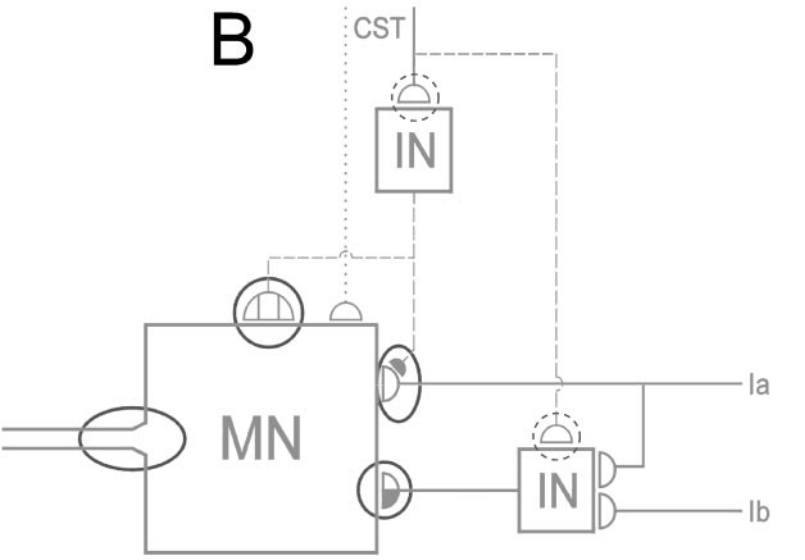
plasticity. A simple laboratory model provides more direct evidence of activity-dependent spinal cord plasticity with skill acquisition.

Skill Acquisition in a Laboratory Model Most of the evidence suggesting that descending and peripheral inputs during development and later in life change the spinal cord consists of changes in spinal cord reflexes, principally SSRs, H-reflexes, and flexion withdrawal reflexes. While these reflexes normally function as parts of complex behaviors, they are in themselves simple behaviors, the simplest behaviors of which the mammalian nervous system is capable, and adaptive changes in them are essentially simple skills that can be used as laboratory models for the plasticity underlying skill acquisition. Operant conditioning of the SSR, or its electrical analog the H-reflex, which has been demonstrated in monkeys, rats, and humans, has furnished clear evidence of activity-dependent spinal cord plasticity and is providing insight into its mechanisms (Wolpaw et al 1983, Evatt et al 1989, Wolpaw 1997).

In the standard protocol, used in monkeys, rats, and humans, SSR or H-reflex amplitude is measured as electromyographic activity, and reward occurs when amplitude is above (for up-training) or below (for down-training) a criterion value. The primary observation is that imposition of the reward criterion changes reflex amplitude appropriately over days and weeks. This adaptive change appears to occur in two phases, a small rapid phase 1 in the first few hours or days and a much slower phase 2 that continues for weeks (Figure 5*A*) (Wolpaw & O'Keefe

Figure 5 Course of training of the spinal stretch reflex (SSR) pathway and associated spinal cord plasticity. (*A*) Two-phase course of SSR up-or down-training in monkeys. Rapid phase 1 change, reflecting appropriate change in descending influence over the reflex arc, occurs within 6 h. Gradual phase 2 change, reflecting spinal cord plasticity produced by the continuation of the altered descending input, develops over at least 40 days. Modified from Wolpaw & O'Keefe (1984). (*B*) Probable sites of spinal cord plasticity and altered descending input with SSR or H-reflex training. "MN" is the motoneuron, and each "IN" is one or more spinal interneuron types. 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 imply the possibility of intervening spinal interneurons, and the dotted pathway is uncertain. The monosynaptic and possibly disynaptic H-reflex pathway from Ia and Ib afferents to the motorneuron is shown. The hypothesized sites of plasticity are circled with solid lines. Starting at the left and moving clockwise, these are: the motoneuron membrane (i.e. firing threshold and axonal conduction velocity), C terminals on the motoneuron, the Ia afferent synaptic connection, and terminals conveying disynaptic group I inhibition or excitation to the motoneuron. The corticospinal tract (CST) is shown, and the probable sites of action of the descending input responsible for the plasticity in the H-reflex pathway are circled with dashed lines. These are: connections on interneurons mediating presynaptic inhibition of the Ia synapse, supplying C terminals to the motoneuron, and/or conveying disynaptic Group I inhibition or excitation to the motoneuron. From Wolpaw (1997).





1984). Phase 1 appears to reflect rapid mode–appropriate change in descending influence over the spinal arc of the reflex, while phase 2 appears to reflect gradual spinal cord plasticity produced by the chronic continuation of the descending input responsible for phase 1. This descending input is conveyed by the corticospinal tract (Chen & Wolpaw 1997, Chen et al 2000). Training is possible in humans with partial spinal cord injuries, but does not seem to occur in those with strokes involving sensorimotor cortex (Segal & Wolf 1994, Segal 1997).

Once established, the reflex asymmetry created by this training survives removal of descending input: It persists after the spinal cord is isolated from the brain (Wolpaw & Lee 1989). Thus, the training changes the spinal cord. This spinal cord plasticity includes changes in motoneuron properties (Carp & Wolpaw 1994, Halter et al 1995, Carp et al 2001). Down-training is accompanied by a positive shift in motoneuron firing threshold and a reduction in axonal conduction velocity. Both changes suggest a positive shift in sodium channel activation voltage, and the change in threshold could account in large part for the smaller reflex. While activity-dependent synaptic plasticity has traditionally received the most attention as the probable basis of learning, the possibility that learning can also involve changes in neuronal voltage-gated ion channels has recently drawn interest (Spitzer 1999). The shift in motoneuron threshold produced by down-training appears to be an example of such neuronally based learning. Additional physiological and anatomical studies suggest that SSR or H-reflex training also affects the Ia afferent–motoneuron synapse, other synaptic terminals on the motoneuron, and interneurons that convey oligosynaptic group 1 input to the motoneuron (Carp & Wolpaw 1995, Feng-Chen & Wolpaw 1996). Down-training and up-training are not mirror images of each other, but rather have different mechanisms. Figure 5*B* summarizes current knowledge of the multi-site spinal cord plasticity produced by SSR or H-reflex training.

SPINAL CORD PLASTICITY AND THE PRODUCTION OF BEHAVIOR

As the preceding sections indicate, clinical and laboratory evidence indicates that activity-dependent plasticity occurs in the spinal cord throughout normal life as well as in response to trauma and disease. The sites of plasticity include synaptic connections made by incoming fibers, interneuronal populations interposed between these inputs and motoneurons, synaptic connections on motoneurons, and the motoneurons themselves. Because spinal motoneurons are, in Sherrington's phrase, "the final common path" for all movements, understanding spinal cord plasticity is central to understanding both simple and complex behaviors (Clarke & O'Malley 1996).

Furthermore, the same attributes responsible for the traditionally inferior status of the spinal cord—separation from the rest of the CNS, simpler structure, obvious role as a connector, and responsibility for simple reflex behaviors—facilitate studies of its plasticity, provide access to supraspinal plasticity, and allow

exploration of how spinal and supraspinal plasticity interact to support acquisition and maintenance of motor skills. The technical accessibility of the spinal cord and its inputs and outputs permit localization and definition of plasticity occurring within it. Moreover, the well-defined pathways that connect it to the rest of the CNS and can be interrupted in the laboratory allow studies to focus on the impact of supraspinal plasticity and the manner in which it generates and interacts with spinal cord plasticity. These advantageous features of the spinal cord clarify fundamental principles of skill acquisition and maintenance and provide guidance for the design and implementation of new methods for restoring function after injury.

A Change in Behavior Involves Plasticity at Multiple Spinal and/or Supraspinal Sites

The fact that activity-dependent plasticity is ubiquitous in the CNS suggests that persistent changes in peripheral or descending input to the spinal cord—whether changes associated with development, skill acquisition (i.e. practice), trauma, or disease—will cause plasticity at multiple sites, both spinal and supraspinal. By taking advantage of the anatomical separation of the spinal cord from the rest of the CNS, several recent studies provide clear examples of behaviors that reflect multi-site activity-dependent plasticity.

A recent study of treadmill locomotion in cats compared the effects on treadmill locomotion of spinalization (i.e. spinal cord transection) followed several weeks later by unilateral denervation of ankle flexor muscles with the effects of denervation followed by spinalization (Carrier et al 1997). Spinalization followed by denervation (or denervation alone) had minimal persistent effects on the pattern or bilateral symmetry of leg movement during locomotion. Increases in hip and knee flexion soon compensated for the decrease in ankle flexion, so that locomotion was only slightly disturbed. In contrast, denervation followed by spinalization produced markedly abnormal and asymmetrical locomotion. After spinalization, the increases in hip and knee flexion that had followed denervation alone were magnified and accompanied by other marked abnormalities in amplitude and timing of muscle activity, so that locomotion was greatly disturbed and did not recover with practice. Figure 6*A* illustrates the difference in muscle activity during locomotion between a cat in which denervation followed spinalization and one in which spinalization followed denervation. The difference implies that the plasticity that occurred after denervation alone and was responsible for the recovery of nearly normal locomotion included modifications at both spinal and supraspinal levels. Spinal and supraspinal plasticity combined to compensate for the effects of denervation. After spinalization removed the influence of the supraspinal plasticity, the spinal cord plasticity functioned by itself, and the result was grossly abnormal spinal locomotion.

Another recent study described a related phenomenon and provided some insight into its mechanism (Whelan & Pearson 1997). During the stance phase of walking in the cat, stimulation of group I afferents in the nerves innervating ankle

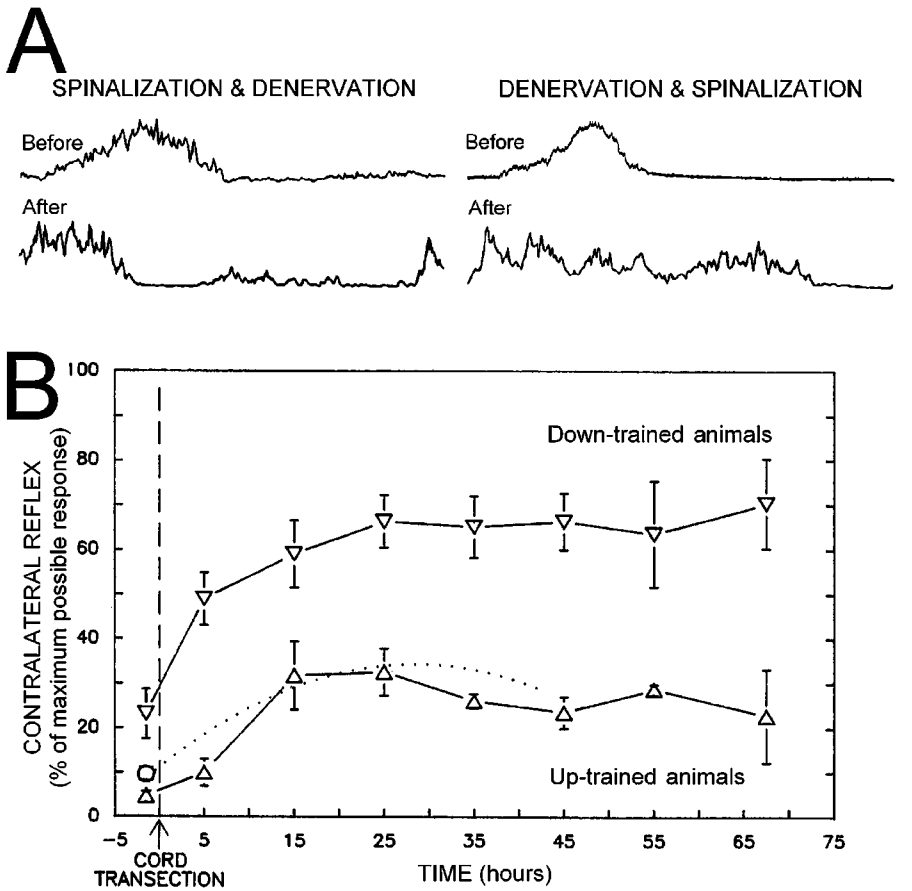


Figure 6 Evidence for multi-site activity-dependent plasticity. (*A*) Timing of muscle activation (i.e. ipsilateral sartorius) during one step cycle of treadmill locomotion in cats before and after denervation followed by spinalization (i.e. spinal cord transection) or spinalization followed by denervation. Timing of activation is nearly normal when denervation follows transection and profoundly abnormal when transection follows denervation. The difference implies that denervation results in both spinal and supraspinal plasticity, which together compensate for the deficit caused by denervation. When spinalization removes the contribution of the supraspinal plasticity so that the spinal cord plasticity functions in isolation, locomotion becomes grossly abnormal. Modified from Carrier et al (1997). (*B*) Contralateral monosynaptic reflex responses (+/− SEM) under anesthesia and with cord transection in monkeys in which the ipsilateral reflex had been increased or decreased by training over 50 days. The contralateral reflexes are much larger in down-trained animals than in up-trained animals [or in naive animals (*open circle* and *dotted line*)]. This finding was unexpected, because in the awake behaving animals the contralateral reflexes had changed little over the course of training. It indicated that training produced plasticity in the contralateral spinal cord that affected behavior only after anesthesia and transection removed descending input and/or suppressed tonic activity in the spinal cord and thereby eliminated the compensatory effect of supraspinal and/or other spinal cord plasticity. (The reflex increase in the first 15 hours is a nonspecific effect of anesthesia and surgery.) Modified from Wolpaw & Lee (1989).

extensor muscles, the LGS nerve to the lateral gastrocnemius and soleus, and the MG nerve to the medial gastrocnemius excites leg extensor muscles and delays the transition to the swing phase. Normally, LGS stimulation is more effective than MG stimulation. However, when the LGS nerve was cut and the cat continued to practice walking on the treadmill, the ability of LGS nerve stimulation to prolong the stance phase decreased to nearly zero over one month, while the effectiveness of MG nerve stimulation increased markedly in 5 days and remained high. Most important, when the cat was spinalized, the decreased effect of LGS nerve stimulation persisted in all cats and the increased effect of MG nerve stimulation persisted in some, indicating that, depending on the cat, spinal cord plasticity was wholly or partly responsible for the changes in the effectiveness of nerve stimulation. Spinal cord plasticity comparable to that revealed here, and/or other denervation-induced spinal cord plasticity, presumably accounted for the profoundly abnormal locomotion that occurred when spinalization followed ankle flexor denervation (Carrier et al 1997) (Figure 6*A*).

As Figure 5*B* summarizes, spinal stretch reflex (SSR) or H-reflex training is associated with plasticity at multiple sites in the ipsilateral spinal cord. Additional evidence that the behavioral effects of this training depend on multi-site plasticity came from measurement of the contralateral reflex in trained monkeys. Over the 50-day course of up-training or down-training of the ipsilateral H-reflex, the contralateral H-reflex remained close to its initial, or control, size (Wolpaw et al 1993). Thus, the behavioral effect of conditioning was focused on the ipsilateral H-reflex. However, when trained monkeys were anesthetized and the spinal cord was transected the contralateral reflex of down-trained animals was at least twice as large as the contralateral reflex of up-trained animals or the reflexes of naive animals (Wolpaw & Lee 1989). As shown in Figure 6*B*, anesthesia and cord transection uncovered a hidden effect of the training: It changed the contralateral side of the spinal cord. In the awake behaving monkey, this plasticity was not apparent, presumably because its effect on the contralateral H-reflex was cancelled out by plasticity at another site, which could be spinal or supraspinal. Anesthesia and spinalization, by removing descending influence and/or by quieting tonic activity in the spinal cord, eliminated the cancelling effect of this additional plasticity and revealed the presence of plasticity that changed the size of the contralateral reflex. What this contralateral plasticity might be and how it might relate to the H-reflex on the trained side are questions as yet unanswered. A similarly puzzling effect occurs in humans who suffer strokes affecting sensorimotor cortex of one hemisphere (Thilmann et al 1990). In addition to the well-known increased reflexes in the contralateral arm, these individuals also display decreased reflexes in the ipsilateral arm. Furthermore, unilateral hindlimb denervation in cats appears to affect contralateral as well as ipsilateral reflexes (Gossard et al 1999).

These clear demonstrations of multi-site plasticity were made possible by the anatomical separation of the spinal cord and by its capacity to produce simple behaviors in reduced preparations and in the presence of deep anesthesia. The unique central position of the spinal cord in the production of almost all behavior provides insight into the origins of multi-site plasticity.

Multi-Site Plasticity is Necessary and Inevitable

That behavioral changes as apparently simple as a larger or smaller H-reflex are associated with plasticity at multiple sites was initially surprising: The common expectation was that a simple change in behavior would be associated with a simple change in the CNS. However, the occurrence of multi-site plasticity appears to be a general principle that applies to even the simplest learning. It has been found as well in other ostensibly simple learning in vertebrate and invertebrate models (Lieb & Frost 1997, Thompson et al 1997, Cohen et al 1997, Lisberger 1998, Garcia et al 1999, Pearson 2000). As discussed below, multi-site plasticity would seem to be both necessary and inevitable, particularly for the spinal cord.

Together with its homologous brainstem nuclei, the spinal cord is the final assembly point for all neuromuscular behaviors, both simple and complex. For example, the motoneurons, interneurons, and synapses in the lumbosacral spinal cord execute all the different forms of locomotion and postural maintenance, produce a variety of specialized movements, withdraw the legs from painful stimuli, participate appropriately in actions involving all four limbs, etc. The fact that the normal spinal cord is able to support these many behaviors satisfactorily, as well as to incorporate new behaviors throughout life, suggests that its neuronal and synaptic function is appropriately adjusted and continually readjusted to accommodate the current behavioral repertoire. That such adjustments occur on a short-term basis as the CNS shifts from one behavior to another or cycles through the different phases of a single behavior is known from studies such as those showing the differences in presynaptic inhibition across standing, walking, and running or the changes that occur in the responses to group I afferent input during the step cycle (Capaday & Stein 1987, Stein 1995, Rossignol 1996, Faist et al 1996, Pearson & Ramirez 1997). The data reviewed in the preceding sections show that long-term adjustments also occur. Activity-dependent plasticity, driven by descending and peripheral inputs, is presumably responsible for maintaining spinal cord circuitry in a functional state appropriate for the execution of its current roster of behaviors. This long-term effect, a consensus produced by the different patterns of activity associated with these different behaviors, serves essentially as a coarse adjustment, establishing ranges over which the fine adjustments specific to each behavior are made. At any point in time, for example, the possible strength of Ia input to soleus motoneurons has a range that includes values appropriate to standing, walking, and running.

In this setting the neural activity that adds a new behavior to the repertoire (whether the activity is produced by daily practice and the behavior is an athletic skill, or the activity results from a peripheral or central lesion and the behavior represents or compensates for a functional deficit) is likely to cause plasticity that accommodates the new behavior as well as plasticity that maintains the old behaviors. For example, the stronger motoneuron response to Ia afferent input that underlies a new behavior (e.g. Figure 4*B*) is likely to affect the many other behaviors that involve primary afferent input to the motoneuron. These effects are

likely to trigger additional activity-dependent plasticity that restores these other behaviors. Furthermore, simply because activity-dependent plasticity can occur at numerous sites in the spinal cord, the changes in activity caused by plasticity that supports the new behavior or maintains old behaviors are likely to trigger additional plasticity at other sites. For example, the larger reflex contralateral to an H-reflex that has been down-trained, evident only with anesthesia and spinal cord transection (Wolpaw & Lee 1989), or the smaller stretch reflexes found in the apparently normal arm contralateral to an arm paralyzed by a hemispheric stroke (Thilmann et al 1990), may represent reactive plasticity caused by change in activity in segmental pathways connecting the right and left sides of the spinal cord. The additional plasticity that maintains a nearly normal contralateral H-reflex in the awake behaving monkey might be compensatory, restoring normal function.

Thus, acquisition of any new behavior, whether it is a skill developed through prolonged practice or an abnormal response associated with supraspinal disease, is likely to involve three categories of plasticity: primary plasticity responsible for the new behavior, compensatory plasticity that maintains previous behaviors despite the impact of the primary plasticity, and reactive plasticity caused by the changes in activity resulting from primary and compensatory plasticity. This etiological categorization helps explain the multi-site plasticity associated with even the simplest change in behavior by indicating that multi-site plasticity is both necessary—to maintain the full repertoire of behaviors—and inevitable—due to the widespread capacity for activity-dependent plasticity. It also helps explain why some examples of plasticity (such as the contralateral spinal cord plasticity with H-reflex training) may bear no apparent relationship to the behavioral change with which they are associated. Furthermore, recognition of these different etiological categories of plasticity helps define factors controlling the effectiveness of therapeutic methods and thus helps guide therapeutic research.

Engagement of Spinal Cord Plasticity in Restoration of Behavior

The ultimate goal of treatment for spinal cord trauma or disease is a spinal cord that once again has normal structure and produces normal behavior. In practice, this single goal separates into two different and not necessarily compatible goals: restoration of normal structure (that is, normal neurons and glia, and intrinsic and extrinsic synaptic connections that display normal strengths and elicit normal neuronal responses) and restoration of normal behavior (that is, the normal repertoire of motor performances). Restoration of structure will guarantee restoration of behavior only if the restoration of structure is complete, is accompanied by restoration of normal peripheral and descending inputs, and is coupled with a comprehensive re-education program that eliminates the plasticity induced by injury or disease and induces the activity-dependent plasticity that occurs during normal development. Partial restoration of structure (for example, normal corticospinal tract connections to motoneurons and interneurons without normal interneuron

connections to motoneurons, or normal interneuron connections without normal distribution of peripheral inputs) or restoration of connections without appropriate activity-dependent adjustment of their strengths is likely to have complex and not necessarily beneficial effects on behavior. Nevertheless, it seems clear that partial restoration of structure and imperfect re-education is all that will be possible in the near future.

At the same time, it is equally clear that restoration of behavior does not necessarily require restoration of normal neuronal and synaptic function. Nearly normal locomotion returns after selective muscle denervation even though the underlying CNS activity is different, and operant conditioning of one H-reflex does not affect the contralateral H-reflex even though the contralateral spinal cord is changed (Carrier et al 1997, Wolpaw & Lee 1989). Restoration of behavior might be achieved without restoration of normal structure. Restoration of useful locomotion or of acceptable bladder, bowel, or sexual function might be achieved more quickly by focusing directly on restoring them rather than focusing on restoring the neuronal and synaptic structure that produced them prior to injury.

In this context, the spinal cord's capacities for activity-dependent plasticity are both a challenge and an opportunity. On the one hand they contribute to the disabilities that follow spinal cord injury and will certainly affect the outcomes of new therapeutic methods that promote regeneration. On the other hand they offer the opportunity to guide restoration of neuronal and synaptic function and should allow imperfect regeneration to support substantial behavioral improvements. For both these reasons, the productive engagement of activity-dependent plasticity in the spinal cord is likely to be a key component of new therapeutic programs for spinal cord injury and other chronic neuromuscular disorders. As the preceding sections indicate, the induction and guidance of activity-dependent spinal cord plasticity requires training protocols that induce appropriate patterns of peripheral and descending inputs to the spinal cord. These protocols may benefit from incorporation of pharmacologic agents and/or artificial or exaggerated sensory inputs and from attention to injury-associated changes in spinal cord elements such as specific receptor populations (e.g. Chau et al 1998, Giroux et al 1999, Muir 1999).

The laboratory development and clinical application of activity-dependent spinal cord plasticity is still at the earliest stage. Explorations of the mechanisms of this plasticity and development of its clinical uses have just begun for locomotion and are still less developed for other important behaviors, such as urination. The methods and results of this work will be greatly affected by what is perhaps the most distinctive feature of activity-dependent spinal cord plasticity as it functions in normal life and in the presence of disease: the slow rate of its effect on behavior. Despite the rapidity of processes such as long-term potentiation, the changes in behavior that result from activity-dependent spinal cord plasticity occur gradually. In the spinal cat the improvements in treadmill locomotion produced by training develop over weeks of daily exposure. Operant conditioning of the SSR or H-reflex in rats, monkeys, or humans occurs gradually over days and weeks. The reflex changes that occur during normal development and those associated with skills such as ballet develop over months and years. This characteristic is, of course,

fortunate—rapid large changes in spinal cord function would wreak havoc with movement control and require prodigious supraspinal compensation.

The characteristically gradual effect of activity-dependent spinal cord plasticity on behavior has practical implications. First and most obviously, laboratory and clinical manipulations and observations of this plasticity need to extend over sufficient time periods. Second, because of the ubiquity of activity-dependent plasticity and the inevitable interaction between primary, compensatory, and reactive types, the concordance between short-term and long-term effects of any intervention (e.g. Figure 5*A*), cannot be assumed in every situation. Short-term gains will not necessarily evolve into long-term improvements. Third, while spinal cord plasticity may support restoration of walking or standing (de Leon 1998b), it may not support the concurrent restoration of both behaviors. The capacity to switch rapidly and appropriately from one behavior to another may require supraspinal participation.

CNS Plasticity and Behavior

The substantial capacity for activity-dependent plasticity in the spinal cord has wide implications. First, as already noted, it suggests that most or all motor skills that are acquired gradually through prolonged practice involve spinal cord plasticity. Thus, these skills cannot be understood or explained simply by studying the changes that occur in cortex, cerebellum, or other supraspinal areas. The changes in the spinal cord need to be defined as well. Second, the fact that these motor skills depend on activity-dependent plasticity throughout the CNS suggests that gradually acquired intellectual skills, such as language mastery or mathematical facility, may also depend on widely distributed plasticity that develops slowly. The rapid changes in behavior that have traditionally engaged most research attention, such as the one-trial acquisition of a new word, may reflect minor adjustments in patterns of plasticity gradually acquired through prolonged practice, adjustments analogous to the change in presynaptic inhibition that accompanies the transition from standing to running, or the alteration in descending influence responsible for phase 1 change in the spinal stretch reflex (Figure 5*A*). Understanding of most skilled behaviors may require exploration of gradually acquired activity-dependent plasticity comparable to the plasticity most readily recognized and studied in the spinal cord.

CONCLUSIONS

The traditional concept of the spinal cord as a hardwired structure that simply provides rapid stereotyped responses to sensory inputs and to commands from the brain is not correct. Ample and diverse evidence indicates that activity-dependent plasticity occurs in the spinal cord during development, with skill acquisition and maintenance later in life, and in response to trauma and disease. In the isolated spinal cord, appropriate peripheral stimuli can produce a variety of persistent effects including habituation, sensitization, several forms of long-term potentiation, and both classical and operant conditioning, and treadmill training regimens

can greatly improve locomotion. Abnormal descending input produced by spinal cord injury or supraspinal disorders gradually changes the spinal cord. Normal descending influence guides development of spinal cord reflexes early in life and throughout later life produces spinal cord plasticity that contributes to skill acquisition and maintenance. The spinal cord plasticity produced by peripheral and descending inputs affects input connections, interneuronal pathways, and motoneurons. Both synaptic and neuronal properties can change, and even simple behavioral changes are associated with changes at multiple spinal and supraspinal sites. This complex plasticity serves to support new behaviors and preserve old behaviors, and also reflects the ubiquity of the capacity for activity-dependent plasticity in the CNS. Engagement of activity-dependent spinal cord plasticity is a key component of new therapeutic approaches to restoring function after spinal cord injury. Appropriate guidance of this plasticity can maximize residual function and will be essential for re-educating a newly regenerated spinal cord. In these practical efforts restoration of useful behaviors might be achieved without full restoration of normal neuronal and synaptic structure, and the typically gradual development of the behavioral effects of activity-dependent spinal cord plasticity will be an important factor. Finally, activity-dependent spinal cord plasticity may help elucidate mechanisms of learning throughout the CNS.

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LITERATURE CITED

Alvares D, Fitzgerald M. 1999. Building blocks of pain: the regulation of key molecules in spinal sensory neurones during development and following peripheral axotomy. *Pain Suppl.* 6:S71–S85

Amar AP, Levy ML. 1999. Pathogenesis and pharmacological strategies for mitigating secondary damage in acute spinal cord injury. *Neurosurgery* 44(5):1027–39

Aminoff MJ. 1993. *Brown-Séquard. A Visionary of Science*, p. 113. New York: Raven. 211 pp.

Angulo-Kinzler RM, Mynark RG, Koceja DM. 1998. Soleus H-reflex gain in elderly and young adults: modulation due to body position. *J. Gerontol. Ser. A* 53(2):M120–25

Baldissera F, Hultborn H, Illert M. 1981. Integration in spinal neuronal systems. In *Handbook of Physiology. Section I: The Nervous System. Vol. II: Motor Control, Part I*, ed.

VB Brooks, pp. 509–95. Baltimore, MD: Williams & Wilkins

Baranauskas G, Nistri A. 1998. Sensitization of pain pathways in the spinalcord: cellular mechanisms. *Prog. Neurobiol.* 54:349–65

Barbeau H, Fung J. 1992. New experimental approaches in the treatment of spastic gait disorders. *Med. Sports Sci.* 36:234–46

Barbeau H, McCrea DA, O'Donovan MJ, Rossignol S, Grill WM, Lemay MA. 1999. Tapping into spinal circuits to restore motor function. *Brain Res. Rev.* 30:27–51

Barbeau H, Rossignol S. 1987. Recovery of locomotion after chronic spinalization in the adult cat. *Brain Res.* 412:84–95

Bélanger M, Drew T, Provencher J, Rossignol S. 1996. A comparison of treadmill locomotion in adult cats before and after spinal transection. *J. Neurophysiol.* 76(1):471–91

Beránek R, Hnik P. 1959. Long-term effects of tenotomy on spinal monosynaptic response in the cat. *Science* 130:981–82

Biering-Sørensen F, Nielans H-M, Dørflinger T, Sørensen B. 1999. Urological situation five years after spinal cord injury. *Scand. J. Urol. Nephrol.* 33:157–61

Boorman G, Hulliger M, Lee RG, Tako K, Tanaka R. 1991. Reciprocal Ia inhibition in patients with spinal spasticity. *Neurosci. Lett.* 127:57–60

Bouyer LJG, Whalen PJ, Pearson KG, Rossignol S. 2001. Adaptive locomoter plasticity in chronic spinal cats following ankle extensor neurectomy. *J. Neurosci.* In press

Bregman BS, Diener PS, McAtee M, Dai HN, James C. 1997. Intervention strategies to enhance anatomical plasticity and recovery of function after spinal cord injury. *Adv. Neurol.* 72:257–75

Brindley GS. 1995. The sacral anterior root stimulator as a means of managing the bladder in patients with spinal cord lesions. *Bailliere's Clin. Neurol.* 4(1):1–13

Brown WF. 1984. *The Physiological and Technical Basis of Electromyography*. Boston, MA: Butterworths

Burke RE. 1998. Spinal cord: Ventral Horn. In *The Synaptic Organization of the Brain*, ed. GM Shepherd, 3:77–120. New York: Oxford Univ. Press

Bussel B, Roby-Brami A, Azouvi P, Biraben A, Yakovleff A, Held JP. 1988. Myoclonus in a patient with spinal cord transection: possible involvement of the spinal stepping generator. *Brain* 111:1235–45

Calancie B, Needham-Shropshire B, Jacobs P, Willer K, Zych G, Green BA. 1994. Involuntary stepping after chronic spinal cord injury: evidence for a central rhythm generator for locomotion in man. *Brain* 117:1143–59

Capaday C, Stein RB. 1987. A method for stimulating the reflex output of a motoneuron pool. *J. Neurosci. Methods* 21:91–104

Carp JS, Wolpaw JR. 1994. Motoneuron plasticity underlying operantly conditioned decrease in primate H-reflex. *J. Neurophysiol.* 72:431–42

Carp JS, Wolpaw JR. 1995. Motoneuron properties after operantly conditioned increase in primate H-reflex. *J. Neurophysiol.* 73:1365–73

Carp JS, Chen XY, Sheikh H, Wolpaw JR. 2001. Operant conditioning of rat H-reflexes affects motoneuron axonal conduction velocity. *Exp. Br. Res.* 136:369–73

Carrier L, Brustein E, Rossignol S. 1997. Locomotion of the hindlimbs after neurectomy of ankle flexors in intact and spinal cats: model for the study of locomotor plasticity. *J. Neurophysiol.* 77:1979–93

Casabona A, Polizzi MC, Perciavalle V. 1990. Differences in H-reflex between athletes trained for explosive contraction and non-trained subjects. *Eur. J. Appl. Physiol.* 61 (1-2):26–32

Chamberlain T, Halick P, Gerard RW. 1963. Fixation of experience in the rat spinal cord. *J. Neurophysiol.* 22:662–73

Chau C, Barbeau H, Rossignol S. 1998. Early locomotor training with clonidine in spinal cats. *J. Neurophysiol.* 79:392–409

Chen D, Nussbaum SB. 2000. The gastrointestinal system and bowel management following

spinal cord injury. *Phys. Med. Rehabil. Clin. N. Am.* 11(1):45–56

Chen HH, Frank E. 1999. Development and specification of muscle sensory neurons. *Curr. Opin. Neurobiol.* 9(4):405–9

Chen XY, Chen L, Wolpaw JR. 2000. The corticospinal tract in development and maintenance of H-reflex operant conditioning in rats. *J. Soc. Neurosci. Abstr.* 26:2206

Chen XY, Wolpaw JR. 1997. Dorsal column but not lateral column transection prevents down conditioning of H-reflex in rats. *J. Neurophysiol.* 78(3):1730–34

Clarke E, Jacyna LS. 1987. *Nineteenth-Century Origins of Neuroscientific Concepts*. Berkeley: Univ. Calif. Press

Clarke E, O'Malley CD. 1996. *The Human Brain and Spinal Cord*. San Francisco: Norman

Cohen TE, Kaplan SW, Kandel ER, Hawkins RD. 1997. A simplified preparation for relating cellular events to behavior: mechanisms contributing to habituation, dishabituation, and sensitization of the Aplysia gill-withdrawal reflex. *J. Neurosci.* 17(8):2886–99

Cope TC, Bodine SC, Fournier M, Edgerton VR. 1986. Soleus motor units in chronic spinal transected cats: physiological and morphological alterations. *J. Neurophysiol.* 55:1202–20

de Groat WC, Kurse MN, Vizzard MA, Cheng C-L, Araki I, Yoshimura N. 1997. Modification of urinary bladder function after spinal cord injury. *Adv. Neurol.* 72:347–64

de Leon RD, Hodgson JA, Roy RR, Edgerton VR. 1999a. Retention of hindlimb stepping ability in adult spinal cats after the cessation of step training. *J. Neurophysiol.* 81:85–94

de Leon RD, Hodgson JA, Roy RR, Edgerton VR. 1998a. Locomotor capacity attributable to step training versus spontaneous recovery after spinalization in adult cats. *J. Neurophysiol.* 79:1329–40

de Leon RD, Hodgson JA, Roy RR, Edgerton VR. 1998b. Full weight-bearing hindlimb standing following stand training in the adult spinal cat. *J. Neurophysiol.* 80:83–91

de Leon RD, Tamaki H, Hodgson JA, Roy RR, Edgerton VR. 1999b Hindlimb locomotor and postural training modulates glycinergic inhibition in the spinal cord of the adult cat. *J. Neurophysiol.* 82:359–69

DeVries HA, Wiswell RA, Romero GT, Heckathorne E. 1985. Changes with age in monosynaptic reflexes elicited by mechanical and electrical stimulation. *Am. J. Phys. Med.* 64:71–81

Dietz V, Colombo G, Jensen L, Baumgartner L. 1995. Locomotor capacity of spinal cord in paraplegic patients. *Ann. Neurol.* 37:574–86

DiGiorgio AM. 1929. Persistenza nell'animale spinale, di asymmetrie posturali e motorie di origine cerebellare: I, II, III. *Arch. Fisiol.* 27:518–80

DiGiorgio AM. 1942. Azione del cervelletto-neocerebellum-sul tono posturale degli arti e localizzazioni cerebellari dell'animale rombencefalico. *Arch. Fisiol.* 42:25–79

Dimitrijevic MR, Gerasimenko Y, Pinter MM. 1998. Evidence for a spinal central pattern generator in humans. *Ann. NY Acad. Sci.* 860:360–76

Dobkin B. 1998. Activity-dependent learning contributes to motor recovery. *Ann. Neurol.* 44(2):158–60

Dobkin B. 1999. Overview of treadmill locomotor training with partial body weight support: a neurophysiologically sound approach whose time has come for randomized clinical trials. *Neurorehab. Neural Repair* 13:157–65

Dobkin B, Harkema S, Requejo PS, Edgerton VR. 1995. Modulation of locomoter-like EMG activity in subjects with complete and incomplete spinal cord injury. *J. Neurol. Rehabil.* 9:183–90

Dubner R, Gold M. 1999. The neurobiology of pain. *Proc. Natl. Acad. Sci. USA* 96:7627–30

Durkovic RG. 1985. Retention of a classically conditioned reflex response in spinal cat. *Behav. Neural Biol.* 43:12–20

Durkovic RG. 1986. The spinal cord: a simplified system for the study of neural mechanisms of mammalian learning and memory. In *Development and Plasticity of the Mammalian Spinal Cord*, ed. ME Goldberger, A Gorio, M Murray, pp. 149–62. Padova: Liviana

Evatt ML, Wolf SL, Segal RL. 1989. Modification of human spinal stretch reflexes: preliminary studies. *Neurosci. Lett.* 105:350–55

Faist M, Dietz V, Pierrot-Deseilligny E. 1996. Modulation, probably presynaptic in origin, of monosynaptic Ia excitation during human gait. *Exp. Brain Res.* 109:441–49

Fawcett JW. 1998. Spinal cord repair: from experimental models to human application. *Spinal Cord* 36(12):811–17

Feng-Chen KC, Wolpaw JR. 1996. Operant conditioning of H-reflex changes synaptic terminals on primate motoneurons. *Proc. Natl. Acad. Sci. USA* 93:9206–11

Field-Fote EC. 2000. Spinal cord control of movement: implications for locomotor rehabilitation following spinal cord injury. *Phys. Ther.* 80(5):477–84

Gallego R, Kuno M, Nunez R, Snider WD. 1979. Disuse enhances synaptic efficacy in spinal mononeurones. *J. Physiol.* 291:191–205

Garcia KS, Steele PM, Mauk MD. 1999. Cerebellar cortex lesions prevent acquisition of conditioned eyelid responses. *J. Neurosci.* 19(24):10940–47

Gerard RW. 1961. The fixation of experience. In *Brain Mechanisms and Learning*, ed. RW Gerard, J Konorski, pp. 21–32. Oxford: Blackwell

Giroux N, Rossignol S, Reader TA. 1999. Autoradiographic study of a1-, a2-noradrenergic and serotonin 1a receptors in the spinal cord of normal and chronically transected cats. *J. Comp. Neurol.* 406:402–14

Giulio L. 1952. Sulla funzione del midollo spinale. Persistenza di asimmetrie da eccitamento labirintico. *Boll. Soc. Ital. Biol. Sper.* 28:1651–52

Goldfarb J, Muller RU. 1971. Occurrence of heteronymous monosynaptic reflexes following tenotomy. *Brain Res.* 28:553–55

Goode DJ, Van Hoven J. 1982. Loss of patellar and Achilles tendon reflex in classical ballet dancers. *Arch. Neurol.* 39:323

Gossard JP, Bouyer LJG, Ménard A, Leblond H. 1999. Plastic changes in the transmission of spinal pathways to pretibial flexors during fictive locomotion following a partial cutaneous denervation in cats. *Neuroscience* 25:1152 (Abstr.)

Halter JA, Carp JS, Wolpaw JR. 1995. Operantly conditioned motoneuron plasticity: possible role of sodium channels. *J. Neurophysiol.* 74:867–71

Harkema S, Hurley SL, Patel UK, Requejo PS, Dobkin B, Edgerton VR. 1997. Human lumbosacral spinal cord interprets loading during stepping. *J. Neurophysiol.* 77:797–811

Henneman E, Mendell LM. 1981. Functional organization of motoneuron pool and inputs. In *Handbook of Physiology. Sect. I. The Nervous System. Vol. II. Motor Control, Part I*, ed. VB Brooks, pp. 423–507. Baltimore, MD: Williams & Wilkins

Herrero JF, Laird JM, Lopez-Garcia JA. 2000. Wind-up of spinal cord neurones and pain sensation: much ado about something? *Prog. Neurobiol.* 61:169–203

Hiersemenzel LP, Curt A, Dietz V. 2000. From spinal shock to spasticity: neuronal adaptations to a spinal cord injury. *Neurology* 54(8):1574–82

Hochman S, McCrea DA. 1994a. Effects of chronic spinalization on ankle extensor motoneurons I. Composite monosynaptic Ia EPSPs in four motoneuron pools. *J. Neurophysiol.* 71(4):1452–67

Hochman S, McCrea DA. 1994b. Effects of chronic spinalization on ankle extensor motoneurons II. Motoneuron electrical properties. *J. Neurophysiol.* 71(4):1468–79

Hochman S, McCrea D. 1994c. Effects of chronic spinalization on ankle extensor motoneurons III. Composite Ia EPSPs in motoneurons separated into motor unit types. *J. Neurophysiol.* 71(4):1480–90

Holmes G. 1915. Spinal injuries of warfare. *Br. Med. J.* 2:815–21

Ince LP, Brucker BS, Alba A. 1978. Conditioned responding of the neurogenic bladder. *Psychosom. Med.* 40(1):14–24

Kandel ER. 1977. Neuronal plasticity and the modification of behavior. In *Handbook of Physiology, Section. I. The Nervous System, Vol. I. Cellular Biology of Neurons*, ed. JM Brookhart, VB Mountcastle, pp. 1137–82. Bethesda, MD: Williams & Wilkins

Kandel ER, Schwartz JH, Jessell TM. 2000. *Principles of Neural Science*. New York: McGraw-Hill

Kiehn O, Harris-Warrick RM, Jordan LM, Hultborn H, Kudo N, eds. 1998. *Neuronal Mechanisms for Generating Locomotor Activity*. New York: NY Acad. Sci.

Koceja DM, Burke JR, Kamen G. 1991. Organization of segmental reflexes in trained dancers. *Int. J. Sports. Med.* 12:285–89

Kozak W, Westerman RA. 1961. Plastic changes of spinal monosynaptic responses from tenotomized muscles in cats. *Nature* 189:753–55

Kuhn RA. 1950. Functional capacity of the isolated human spinal cord. *Brain* 1:1–51

Levinsson A, Luo XL, Holmberg H, Schouenborg J. 1999. Developmental tuning in a spinal nociceptive system: effects of neonatal spinalization. *J. Neurosci.* 19(23):10397–403

Liddell EGT. 1960. *The Discovery of Reflexes*. Oxford: Clarendon

Lieb JR, Frost WN. 1997. Realistic simulation of the Aplysia siphon-withdrawal reflex circuit: roles of circuit elements in producing motor output. *J. Neurophysiol.* 77(3):1249–68

Linsenmeyer TD. 2000. Sexual function and infertility following spinal cord injury. *Phys. Med. Rehabil. Clin. N. Am.* 11(1):141–56

Lisberger SG. 1998. Physiologic basis for motor learning in the vestibulo-ocular reflex. *Otolaryngol.-Head Neck Surg.* 119(1):43–48

Liu X, Sandkühler J. 1997. Characterization of long-term potentiation of C-fiber-evoked potentials in spinal dorsal horn of adult rat: essential role of NK1 and NK2 receptors. *J. Neurophysiol.* 78(4):1973–82

Lloyd DPC. 1949. Post-tetanic potentiation of response in monosynaptic reflex pathways of the spinal cord. *J. Gen. Physiol.* 33:147–70

Lovely RG, Gregor RJ, Roy RR, Edgerton VR. 1986. Effects of training on the recovery of full-weight-bearing stepping in the adult spinal cat. *Exp. Neurol.* 92:421–35

Magladery JW, Porter WE, Park AM, Teasdall RD. 1951. Electrophysiological studies of nerve and reflex activity in normal man. IV. The two-neuron reflex and identification of certain action potentials from spinal roots and cord. *Bull. John Hopkins Hosp.* 88:499–519

Manni E. 1950. Localizzazoni cerebellari corticali nella cavia. Nota 1: Il "corpus cerebelli". *Arch. Fisiol.* 49:213–37

Matthews PBC. 1972. *Mammalian Muscle Receptors and Their Central Actions*, pp. 319–409. Baltimore, MD: Williams & Wilkins

McKinley WO, Jackson AB, Cardenas DD, DeVivo MJ. 1999. Long-term medical complications after traumatic spinal cord injury: a regional model systems analysis. *Arch. Phys. Med. Rehabil.* 80(11):1402–10

Mendell LM. 1984. Modifiability of spinal synapses. *Phys. Rev.* 64:260–324

Mendell LM. 1988. Physiological aspects of synaptic plasticity: the Ia/motoneuron connection as a model. *Adv. Neurol.* 47:337–60

Mendell LM. 1999. Neurotrophin action on sensory neurons in adults: an extension of the neurotrophic hypothesis. *Pain* Suppl. 6:S127–32

Mendell LM, Wall PD. 1965. Response of single dorsal cells to peripheral cutaneous unmyelinated fibers. *Nature* 206:97–99

Meyer-Lohmann J, Christakos CN, Wolf H. 1986. Dominance of the short-latency component in perturbation induced electromyographic responses of long-trained monkeys. *Exp. Brain Res.* 64:393–99

Monga M, Bernie J, Rajasekaran M. 1999. Male infertility and erectile dysfunction in spinal

cord injury: A review. *Arch. Phys. Med. Rehabil.* 80:1331–39

Mountcastle VB. 1980. Effects of spinal cord transection. In *Medical Physiology*, ed. VB Mountcastle, 1:781–86. St. Louis: Mosby

Muir GD. 1999. Locomotor plasticity after spinal injury in the chick. *J. Neurotrauma* 16(8):705–10

Muir GD, Steeves JD. 1995. Phasic cutaneous input facilitates locomotor recovery after spinal cord injury in the chick. *J. Neurophysiol.* 74:358–68

Muir GD, Steeves JD. 1997. Sensorimotor stimulation to improve locomotor recovery after spinal cord injury. *Trends Neurosci.* 20(2):72–77

Munson JB, Foehring RC, Lofton SA, Zengel JE, Sypert GW. 1986. Plasticity of medial gastrocnemius motor units following cordotomy in the cat. *J. Neurophysiol.* 55:619–34

Myklebust BM, Gottlieb GL, Agarwal GC. 1986. Stretch reflexes of the normal human infant. *Dev. Med. Child Neurol.* 28:440–49

Myklebust BM, Gottlieb GL, Penn RL, Agarwal GC. 1982. Reciprocal excitation of antagonistic muscles as a differentiating feature in spasticity. *Ann. Neurol.* 12:367–74

Nelson SG, Mendell LM. 1979. Enhancement in Ia-motoneuron synaptic transmission caudal to chronic spinal cord transection. *J. Neurophysiol.* 42:642–54

Neuburger M. 1981. Experiments on the reflex mechanism. In *The Historical Development of Experimental Brain and Spinal Cord Physiology before Flourens*, ed. M Neuberger, E Clarke, pp. 237–46. Baltimore: The Johns Hopkins Univ. Press

Nielsen J, Crone C, Hultborn H. 1993. H-reflexes are smaller in dancers from the Royal Danish Ballet than in well-trained athletes. *Eur. J. Appl. Physiol.* 66:116–21

Orlovsky GN, Deliagina TG, Grillner S. 1999. *Neuronal Control of Locomotion from Mollusc to Man*. New York: Oxford Univ. Press

O'Sullivan MC, Eyre JA, Miller S. 1991. Radiation of phasic stretch reflex in biceps brachii to muscles of the arm in man and its restriction during development. *J. Physiol.* 439:529–43

Patterson MM. 1976. Mechanisms of classical conditioning and fixation in spinal mammals. In *Advances in Psychobiology*, ed. LM Aanonsen, RF Thompson, 10:381–436. New York: Wiley

Pearson KG. 2000. Plasticity of neuronal networks in the spinal cord: modifications in response to altered sensory input. *Prog. Br. Res.* 128:61–70

Pearson KG, Ramirez JM. 1997. Sensory modulation of pattern-generating circuits. In *Neurons, Networks and Motor Behavior*, ed. PSG Stein et al, 225–35. Cambridge Mass: MIT Press. 305 pp.

Peckham PH, Creasey GH. 1992. Neural prostheses: clinical application of functional electrical stimulation in spinal cord injury. *Paraplegia* 30:96–101

Pockett S. 1995. Spinal cord synaptic plasticity and chronic pain. *Anest. Analg.* 80:173–79

Randić M. 1996. Plasticity of excitatory synaptic transmission in the spinal cord dorsal horn. *Prog. Brain Res.* 113:463–506

Reschke MF, Anderson DJ, Homick JL. 1986. Vestibulo-spinal response modification as determined with the H-reflex during the Spacelab-1 flight. *Exp. Brain Res.* 64:367–79

Riddoch G. 1917. The reflex functions of the completely divided spinal cord in man, compared with those associated with less severe lesions. *Brain* 40:264–402

Rijkhoff NJM, Wijkstra H, Van Kerrebroeck PEV, Debruyne FMJ. 1997. Urinary bladder control by electrical stimulation techniques in spinal cord injury. *Neurourol. Urodyn.* 16:39–53

Robbins A, Nelson PG. 1970. Tenotomy and the spinal monosynaptic reflex. *Exp. Neurol.* 27:66–75

Rochcongar P, Dassonville J, Le Bars R. 1979. Modifications du reflexe de Hoffmann en fonction de l'entrainement chez le sportif. *Eur. J. Appl. Physiol.* 40:165–70

Ronthal M. 1998. Spinal cord injury. In *Clinical*

Neurology, ed. RJ Joynt, RC Griggs, 47:1–28. Hagerstown, MD: Lippincott Williams & Wilkins

Rossignol S. 1996. Neural control of stereotypic limb movements. In *Handbook of Physiology*, ed. LB Rowell, JT Sheperd, pp. 173–216. New York: Oxford Univ. Press

Rossignol S. 2000. Locomotion and its recovery after spinal injury. *Curr. Opin. Neurobiol.* 10:708–16

Rossignol S, Bouyer LJG. 2001. Locomoter compensation to peripheral nerve lesions in the cat. In *Spinal Cord Plasticity: Alterations in Reflex Function*, ed. MM Patterson, JW Grau. Boston: Kluwer Acad.

Roy RR, Acosta L. 1986. Fiber type and fiber size changes in selected thigh muscles six months after low thoracic spinal cord transection in adult cats: exercise effects. *Exp. Neurol.* 92:675–85

Roy RR, Baldwin KM, Edgerton VR. 1991. The plasticity of skeletal muscle: effects of neuromuscular activity. *Exerc. Sport Sci. Rev.* 19:269–312

Roy RR, Talmadge RJ, Hodgson JA, Zhong H, Baldwin KM, Edgerton VR. 1998. Training effects on soleus of cats spinal cord transected (T12-13) as adults. *Muscle Nerve* 21:63–71

Sabbahi MA, Sedgwick EM. 1982. Age-related changes in monosynaptic reflex excitability. *J. Gerontol.* 37(1):24–32

Segal RL. 1997. Plasticity in the central nervous system: operant conditioning of the spinal stretch reflex. *Top. Stroke Rehabil.* 3(4):76–87

Segal RL, Wolf SL. 1994. Operant conditioning of spinal stretch reflex in patients with spinal cord injuries. *Exp. Neurol.* 130:202–13

Shefner JM, Berman SA, Sarkarati M, Young RR. 1992. Recurrent inhibition is increased in patients with spinal cord injury. *Neurology* 42:2162–68

Shurrager PS, Dykman RA. 1951. Walking spinal carnivores. *J. Comp. Physiol. Psychol.* 44:252–62

Spitzer NC. 1999. New dimensions of neuronal plasticity. *Nat. Neurosci.* 2(6):489–91

Stein RB. 1995. Presynaptic inhibition in humans. *Prog. Neurobiol.* 47:533–44

Stein RB. 1999. Functional electrical stimulation after spinal cord injury. *J. Neurotrauma* 16(8):713–17

Stiens SA, Bergman SB, Goetz LL. 1997. Neurogenic bowel dysfunction after spinal cord injury: clinical evaluation and rehabilitative management. *Arch. Phys. Med. Rehabil.* 78:S86–102

Straka H, Dieringer N. 1995. Spinal plasticity after hemilabyrinthectomy and its relation to postural recovery in the frog. *J. Neurophysiol.* 73:1617–31

Tai Q, Goshgarian HG. 1996. Ultrastructural quantitative analysis of glutamatergic and GABAergic synaptic terminals in the phrenic nucleus after spinal cord injury. *J. Comp. Neurol.* 372(3):343–55

Tai Q, Palazzolo KL, Goshgarian HG. 1997. Synaptic plasticity of 5-hydroxytrypamine-immunoreactive terminals in the phrenic nucleus following spinal cord injury: a quantitative electron microscopic analysis. *J. Comp. Neurol.* 386(4):613–24

Teasell RW, Arnold JM, Krassioukov A, Delaney GA. 2000. Cardiovascular consequences of loss of supraspinal control of the sympathetic nervous system after spinal cord injury. *Arch. Phys. Med. Rehabil.* 81(4):506–16

Thilmann A, Fellows S, Garms E. 1990. Pathological stretch reflexes on the "good" side of hemiparetic patients. *J. Neurol. Neurosurg. Psychiatry* 53(3):208–14

Thompson FJ, Reier PJ, Lucas CC, Parmer R. 1992. Altered patterns of reflex excitability subsequent to contusion injury of the rat spinal cord. *J. Neurophysiol.* 68:1473–86

Thompson RF. 2001. Spinal plasticity. In *Spinal Cord Plasticity: Alterations in Reflex* Function, ed. MM Patterson, JW Grau. Boston: Kluwer Acad.

Thompson RF, Bao S, Chen L, Cipriano BD,

Grethe JS, et al. 1997. Associative learning. *Int. Rev. Neurobiol.* 41:151–89

Trimble MH, Koceja DM. 1994. Modulation of the triceps surae H-reflex with training. *Int. J. Neurosci.* 76:293–303

Tuszynski MH, Kordower JE. 1999. *CNS Regeneration-Basic Science and Clinical Advances*. San Diego: Academic

Van Kerrebroeck PEV. 1998. The role of electrical stimulation in voiding dysfunction. *Eur. J. Urol.* 34(Suppl. 1):27–30

Webb CB, Cope TC. 1992. Modulation of Ia EPSP amplitude: the effects of chronic synaptic inactivity. *J. Neurosci.* 12:338–44

Weld KJ, Dmochowski RR. 2000. Effect of bladder management on urological complications in spinal cord injured patients. *J. Urol.* 163:768–72

Wernig A, Muller S, Nanassy A, Cagol E. 1995. Laufband therapy based on "rules of spinal locomotion" is effective in spinal cord injured persons. *Eur. J. Neurosci.* 7:823–29

Wernig A, Nanassy A, Muller S. 1998. Maintenance of locomotor abilities following Laufband (treadmill) therapy in para- and tetraplegic persons: follow-up studies. *Spinal Cord* 36(11):744–49

Whelan PJ, Pearson KG. 1997. Plasticity in reflex pathways controlling stepping in the cat. *J. Neurophysiol.* 78(3):1643–50

Wilson P, Kitchener PD. 1996. Plasticity of cutaneous primary afferent projections to the spinal dorsal horn. *Prog. Neurobiol.* 48:105–29

Wolpaw JR. 1997. The complex structure of a simple memory. *Trends Neurosci.* 20:588–94

Wolpaw JR, Braitman DJ, Seegal RF. 1983. Adaptive plasticity in the primate spinal stretch reflex: initial development. *J. Neurophysiol.* 50:1296–311

Wolpaw JR, Herchenroder PA, Carp JS. 1993. Operant conditioning of the primate H-reflex: factors affecting the magnitude of change. *Exp. Brain Res.* 97:31–39

Wolpaw JR, Lee CL. 1989. Memory traces in primate spinal cord produced by operant conditioning of H-reflex. *J. Neurophysiol.* 61:563–72

Wolpaw JR, O'Keefe JA. 1984. Adaptive plasticity in the primate spinal stretch reflex: evidence for a two-phase process. *J. Neurosci.* 4:2718–24

Woolf CJ, Costigan M. 1999. Transcriptional and posttranslational plasticity and the generation of inflammatory pain. *Proc. Natl. Acad. Sci. USA* 96:7723–30

Yaksh TL, Hua X-Y, Kalcheva I, Nozaki-Taguchi N, Marsala M. 1999. The spinal biology in humans and animals of pain states generated by persistent small afferent input. *Proc. Natl. Acad. Sci. USA* 96:7680–86

Yamanaka K, Yamamoto S, Nakazawa K, Yano H, Suzuki Y, Fukunaga T. 1999. The effects of long-term bed rest on H-reflex and motor evoked potential in the human soleus muscle during standing. *Neurosci. Lett.* 266:101–4

Yoshimura N. 1999. Bladder afferent pathway and spinal cord injury: possible mechanisms inducing hyperreflexia of the urinary bladder. *Prog. Neurobiol.* 57:583–606

Zheng Z, Gibson SJ, Khalil Z, Helme R, McMeeken JM. 2000. Age-related differences in the time course of capsaicin-induced hyperalgesia. *Pain* 85:51–58

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