What Can the Spinal Cord Teach Us about Learning and Memory?

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Abstract

The work of recent decades has shown that the nervous system changes continually throughout life. Activity-dependent central nervous system (CNS) plasticity has many different mechanisms and involves essentially every region, from the cortex to the spinal cord. This new knowledge radically changes the challenge of explaining learning and memory and greatly increases the relevance of the spinal cord. The challenge is now to explain how continual and ubiquitous plasticity accounts for the initial acquisition and subsequent stability of many different learned behaviors. The spinal cord has a key role because it is the final common pathway for all behavior and is a site of substantial plasticity. Furthermore, because it is simple, accessible, distant from the rest of the CNS, and directly connected to behavior, the spinal cord is uniquely suited for identifying sites and mechanisms of plasticity and for determining how they account for behavioral change. Experimental models based on spinal cord reflexes facilitate study of the gradual plasticity that makes possible most rapid learning phenomena. These models reveal principles and generate concepts that are likely to apply to learning and memory throughout the CNS. In addition, they offer new approaches to guiding activity-dependent plasticity so as to restore functions lost to injury or disease.

Keywords

activity dependent, plasticity, conditioning, motor control, motor skill, operant, sensorimotor cortex, corticospinal tract, H-reflex, spinal reflex

The title of this review asks a question. Until recently, "Not much!" was a plausible response. That is no longer true. The discoveries of the past 30 years have dissolved the traditional image of a hardwired nervous system that changes rarely and only in a few locations. It is now clear that activity-dependent plasticity occurs continually throughout the central nervous system (CNS) and throughout life and has many different mechanisms. This realization has profoundly changed the scientific challenge presented by the phenomena of learning and memory. In addition, it has moved the spinal cord into the center of the challenge, both as a key part of the problem and as an invaluable opportunity for addressing it.

To answer the question that the title asks, this paper first describes the new challenge, the research strategy that has arisen in response, and the central position that the spinal cord now occupies. It then goes on to review the insights provided by a spinal cord model and considers their implications for understanding learning and memory as well as for restoring CNS functions lost to injury or disease.

The Challenge

While learning and memory have a long and complex history in philosophy, their place in contemporary neuroscience is straightforward (Wolpaw 2002, for review). As presently understood, the function of the CNS is to produce appropriate behavior. Behavior is determined in large part by experience, both current experience and experience that occurred in the past, even in the remote past. Learning and memory encompass the still largely obscure phenomena responsible for the effects of past experiences on behavior.

When the CNS was thought to be hardwired and inflexible, the challenge of explaining learning and memory, although technically daunting, was theoretically straightforward: the challenge was to find the few special

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sites where plasticity occurs in response to experience and to describe what changes. This challenge gave rise to the traditional *localization* research strategy, which sought to find the change in the nervous system responsible for learning. The assumption, supported by the concept of the hardwired CNS, was that the change would be very localized and would entirely account for the learning.

However, it is now apparent that the neural activity produced by experience can have many different lasting effects. These effects include synaptic plasticity such as sprouting, long-term potentiation (LTP), and long-term depression (LTD), neuronal plasticity such as neurogenesis, gene activation, dendritic modifications, and changes in physiological properties, and glial, vascular, and humoral plasticity as well (Isaacs and others 1992; Lindholm and others 1994; Marder and others 1996; Palmer and others 2000; Waxman 2000; Wolpaw and Tennissen 2001; Cantrell and Catterall 2001; Carr and others 2003; Zhang and Linden 2003; Destexhe and Marder 2004; Chen and Ghosh 2005; Lledo and Saghatelyan 2005; Xu and Kang 2005; Bellamy and Ogden 2006; Tropea and others 2006; Bruel-Jungerman and others 2007a, 2007b; Guo and others 2007; Koh and Weiss 2007; Tashiro and others 2007; Whitaker and others 2007; Bakkum and others 2008; Bramham 2008; Cohen and Fields 2008; Falvell and Greenberg 2008; Ge and others 2008; Knott and Holtmaat 2008; Kuczewski and others 2008, 2009; Lange-Asschenfeldt and Kojda 2008; Tan and others 2008; Theodosis and others 2008; Balakrishnan and Bellamy 2009; Butz and others 2009; Chen and others 2010; Holtmaat and Svoboda 2009; Johnson 2009; Lushnikova and others 2009; Ma and others 2009). Furthermore, these changes can occur throughout the CNS from the cortex to the spinal cord. Particularly striking examples of plasticity at subcortical and spinal levels include the changes in the basal ganglia associated with motor learning (Graybiel 2005; Kreitzer and Makenka 2008; Wickens 2009), the extensive brain stem modifications induced by auditory stimulation regimes (Illing 2001), and the physiological and histochemical effects of treadmill training on the isolated spinal cord (Rossignol and others 2002; Courtine and others 2009).

This new reality, the ubiquity and variety of CNS plasticity, greatly complicates the challenge of explaining how past experience affects present behavior. First, the sites where plasticity is now most commonly studied, such as the hippocampus and the neocortex, connect to behavior only through other CNS regions that are also capable of plasticity. Thus, even if a particular hippocampal or neocortical change correlates with learning, the role of that change in a learned behavior is likely to depend on interactions with changes elsewhere. Second, because learning continues throughout life and because activity-dependent plasticity is ubiquitous in the CNS, the plasticity that underlies a newly learned behavior is likely to affect previously learned behaviors and will thereby lead to additional plasticity that serves to preserve these older behaviors. Third, because the changes responsible for a new behavior or for preserving older behaviors are likely to affect ongoing CNS activity, they will probably induce still more plasticity.

In sum, even the simplest learning experience is likely to produce a complex pattern of plasticity involving changes of many kinds in many places. Some of these changes will contribute to the learned behavior, while others will be unrelated to it or may even appear to detract from it. The central challenge is to explain the learned behavior, to explain how the various changes combine to produce the behavior. The challenge, in short, is to link the plasticity to the learning. This challenge is driving a transition from the traditional localization strategy to a newer *mechanistic* strategy.

The Mechanistic Strategy

In contrast to the localization strategy, which simply seeks plasticity associated with learning, the newer mechanistic strategy tries to explain the learned behavior, that is, to explain how the plasticity produced by the experience actually accounts for the behavior. This strategy is practical mainly for very simple learned behaviors produced by defined and accessible neural circuitry. In such models, it should be possible to localize and describe the changes in neural function that directly underlie the behavioral impact of the learning, to determine where and how the learning changes the behavior. The typical experimental protocol administers a stimulus that elicits the behavior and observes where and how the activity in the circuitry leading from the stimulus to the behavior differs before and after the learning experience.

The mechanistic strategy has been pursued energetically in invertebrate models, such as the gill and siphon withdrawal responses to tactile stimulation in *Aplysia,* and in vertebrate models, such as the vestibulo-ocular reflex (VOR) and the conditioned eye-blink response. This work has yielded both new knowledge of the plasticity associated with learning and new appreciation of the difficulty of explaining exactly how the plasticity accounts for the learning (Green and Woodruff-Pak 2000; Steinmetz 2000; Croll 2003; Blazquez and others 2004; Broussard and Kassardjian 2004; Leonard and Edstrom 2004; De Zeeuw and Yeo 2005; Delgado-Garcia and Gruart 2006).

However, little attention has been given to the spinal cord as a particularly promising venue for the mechanistic strategy. This blind spot reflects the persistent influence of the archaic belief that the spinal cord is capable

only of fixed reflex patterns (Wolpaw and Tennissen 2001). In reality, mechanistic models based on behaviors mediated by spinal cord pathways have distinct advantages for studying learning and memory.

The Advantages of the Spinal Cord

Activity-dependent plasticity is abundant in the vertebrate spinal cord (Mendell 1984; Parker 2000; Wolpaw and Tennissen 2001; Rossignol and others 2002; Willis 2002; Dobkin and Havton 2004; Rygh and others 2005, 2006; Adkins and others 2006; Zhang and others 2006; Martin and others 2007; Dunlop 2008; Fouad and Tse 2008; Lynskey and others 2008; Courtine and others 2009; Sadowski and McDonald 2009). Inputs from the brain and the periphery change the spinal cord during development, throughout later life, and in response to trauma and disease. This spinal cord plasticity combines with brain plasticity to produce normal learned behaviors (or "skills") and to shape the complex disabilities caused by disorders like spinal cord injury.

The relative simplicity and accessibility of the spinal cord and its distance from the brain facilitate study of the individual elements of the multisite plasticity that underlies even the simplest learning. The major neuronal populations and pathways of the spinal cord are well known. Its connections, both those with the periphery and those with the brain, are accessible to monitoring and to direct excitation, as well as to short-term or long-term interruption. Furthermore, because the spinal cord is directly connected to behavior, the task of linking its plasticity to behavior is easier than it is for other CNS regions. These are major experimental advantages, the same advantages that explain why much of what is currently known of CNS physiology and anatomy came originally from spinal cord studies.

Also important is the simple fact that spinal cord pathways participate in essentially all behaviors, for the spinal cord and its motoneurons (and the analogous brain stem nuclei) are, in Sherrington's term, the "final common pathway" (Clarke and O'Malley 1996). It is in the spinal cord that multiple central and peripheral influences coalesce into the motoneuron activations that produce behavior. Thus, spinal cord plasticity is likely to contribute to many learned behaviors, and its exploration is an essential part of understanding them.

Finally, activity-dependent spinal cord plasticity contributes, for good or ill, to the functional impact of many chronic neuromuscular disorders such as spinal cord injury, cerebral palsy, and stroke (O'Sullivan and others 1998; Wolpaw and Tennissen 2001; Martin and others 2007; Raineteau 2008; Lapash Daniels and others 2009). Thus, exploring this plasticity may lead to effective new methods for improving neuromuscular function after trauma or disease.

Using a Spinal Cord Reflex to Study Learning and Memory

Spinal cord reflexes are simple behaviors produced by pathways that are entirely within the spinal cord. The sensory afferents that elicit these reflexes activate spinal motoneurons directly or through spinal interneurons. While the pathways are wholly spinal, they are influenced by descending inputs from the brain directly or through spinal interneurons. In the short term, the brain adjusts these reflexes to the needs of different actions (e.g., standing or walking or running [Stein 1995]). In the long term, the brain gradually shapes reflexes during development, during skill acquisition later on, and in response to trauma and disease (Wolpaw and Tennissen 2001; Wolpaw 2006). These long-term changes include activity-dependent plasticity in the spinal cord itself. Spinal cord reflexes, the brain's long-term influence over them, and the spinal cord plasticity this influence produces can be the basis for powerful experimental models of learning and memory.

One such model has focused on operant conditioning of the simplest spinal cord reflex, the spinal stretch reflex (SSR) (i.e., the "knee-jerk" reflex), or its electrical analog, the H-reflex (Wolpaw and others 1983; Wolpaw 1987; Evatt and others 1989; Chen and Wolpaw 1995; Carp and others 2006; Wolpaw and Chen 2009; Thompson and others 2009). These reflexes are produced mainly by the two-neuron monosynaptic pathway comprised of the primary afferent fiber from the muscle spindle, its synapse on the spinal motoneuron, and the motoneuron (Magladery and others 1951; Matthews 1972; Baldissera and others 1981; Henneman and Mendell 1981; Brown 1984; Zehr 2002; Knikou 2008). This pathway is illustrated in Figure 1. In the SSR, the afferent is excited by sudden muscle stretch; in the H-reflex, it is excited by electrical stimulation of the nerve. The standard experimental protocol rewards the subject (whether monkey, rat, mouse, or human) for a larger or smaller reflex and thereby operantly conditions the subject to produce descending influence that is appropriate to the reward contingency (i.e., influence that increases or decreases reflex size). In this laboratory version of the brain's long-term shaping of spinal reflexes in normal life, the continued maintenance of this appropriate descending influence causes plasticity in the spinal pathway of the reflex and thus changes the size of the reflex appropriately.

Figure 2A shows the H-reflex operant conditioning protocol as it is implemented in rats and humans (Chen and Wolpaw 1995; Thompson and others 2009). The monkey and mouse protocols are similar (Wolpaw and

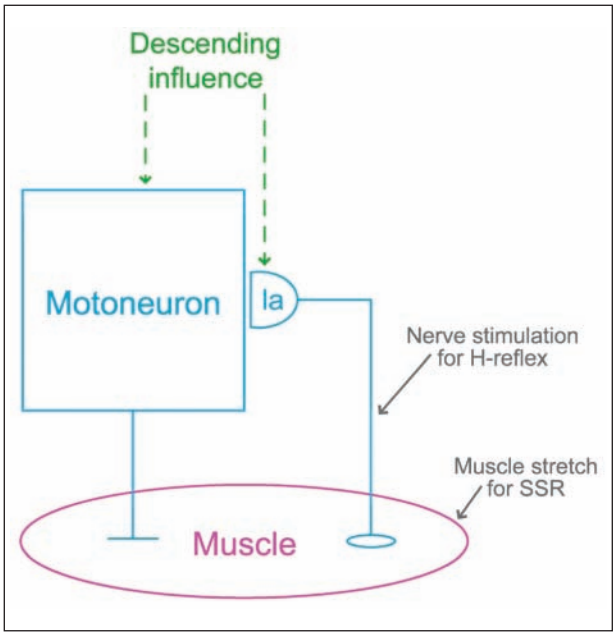

Figure 1. The principal pathway of the spinal stretch reflex (SSR) and its electrical analog, the H-reflex. The pathway consists of the primary afferent neuron from the muscle spindle, its synapse on the alpha motoneuron, and the motoneuron itself. When the afferent is excited, it excites the motoneurons innervating the same muscle and its synergists. If the afferent is excited in the normal way, that is, by muscle stretch, the muscle's response is the SSR. If it is excited by an electrical stimulus, the response is the H-reflex. The SSR and the H-reflex are measured by electromyography (EMG) or by their kinematic effects. While their pathway is entirely spinal, both reflexes are affected by descending influences on the primary afferent synapse (exerted presynaptically) and on the motoneuron, and the SSR is also affected by descending control of spindle sensitivity. As a result of this descending influence and the plasticity it induces in the spinal cord, the brain can gradually modify these spinal reflexes so as to increase the number of rewards. From Wolpaw 1997.

Herchenroder 1990; Carp and others 2006). The sequence of events in a trial is the same in each species. First, background muscle activity (EMG) remains in a specific range for several seconds. Second, nerve stimulation just above the threshold of the M-wave elicits the M-wave (i.e., the muscle response elicited by direct excitation of motor axons) and the H-reflex. Third, if the protocol is in the up-conditioning (HRup) or down-conditioning (HRdown) mode, a reward occurs whenever H-reflex size is above (HRup) or below (HRdown) a criterion value. Because the H-reflex is the earliest possible CNS response to the nerve stimulus, the subject can modify H-reflex size only by being prepared ahead of time, that is, by maintaining mode-appropriate descending influence over the spinal pathway of the reflex. It is this descending influence that gradually causes the activity-dependent spinal cord plasticity that underlies H-reflex change.

The central finding is that the HRup or HRdown mode changes the size of the reflex appropriately over days and weeks. According to a standard definition of a skill as an adaptive behavior acquired through practice (Compact OED 1993), the larger (HRup mode) or smaller (HRdown mode) H-reflex created by this operant conditioning protocol is a simple motor skill. Figure 2B shows the gradual H-reflex increases and decreases as they occur in rats and humans, and Figure 2C shows examples of the reflex changes that are eventually produced. (Results in monkeys and mice are comparable [Wolpaw and others 1993; Carp and others 2006].) Detailed analyses (Wolpaw and O'Keefe 1984; Chen and others 2001; Thompson and others 2009) show that the reflex change occurs in 2 phases, a small rapid phase 1 change that occurs in the first few days (in animals) or sessions (in humans) and a much slower phase 2 change that progresses over weeks. Phase 1 probably results from a relatively rapid mode-appropriate change in descending influence that is operantly conditioned by the reward contingency. In contrast, phase 2 appears to reflect gradual spinal cord plasticity caused by the chronic continuation of the appropriate descending influence. Animal studies show that this spinal cord plasticity persists for some days after all descending influence is removed (Wolpaw and Lee 1989), and they thereby confirm that conditioning changes the spinal cord.

The Complex Plasticity Associated with Reflex Conditioning

H-reflex conditioning is accompanied by many changes in the spinal cord. Down-conditioning causes a positive shift in motoneuron firing threshold and a fall in axonal conduction velocity (Carp and Wolpaw 1994; Carp and others 2001) (Fig. 3A and 3B). Taken together, these 2 changes suggest that a positive shift in sodium-channel activation voltage occurs throughout the motoneuron soma and axon (Halter and others 1995). The change in threshold can explain both the smaller H-reflex and the drop in conduction velocity. While synaptic plasticity is commonly assumed to be the primary mechanism of learning, the shift in motoneuron threshold caused by down-conditioning seems to be an example of a neuronal mechanism (Zhang and Linden 2003).

In addition to this neuronal plasticity, H-reflex conditioning also modifies several different populations of synaptic terminals on the motoneuron, and it affects spinal interneurons (Wolpaw and Tennissen 2001; Wolpaw 2006, for review). The effects on GABAergic terminals and GABAergic interneurons are particularly striking

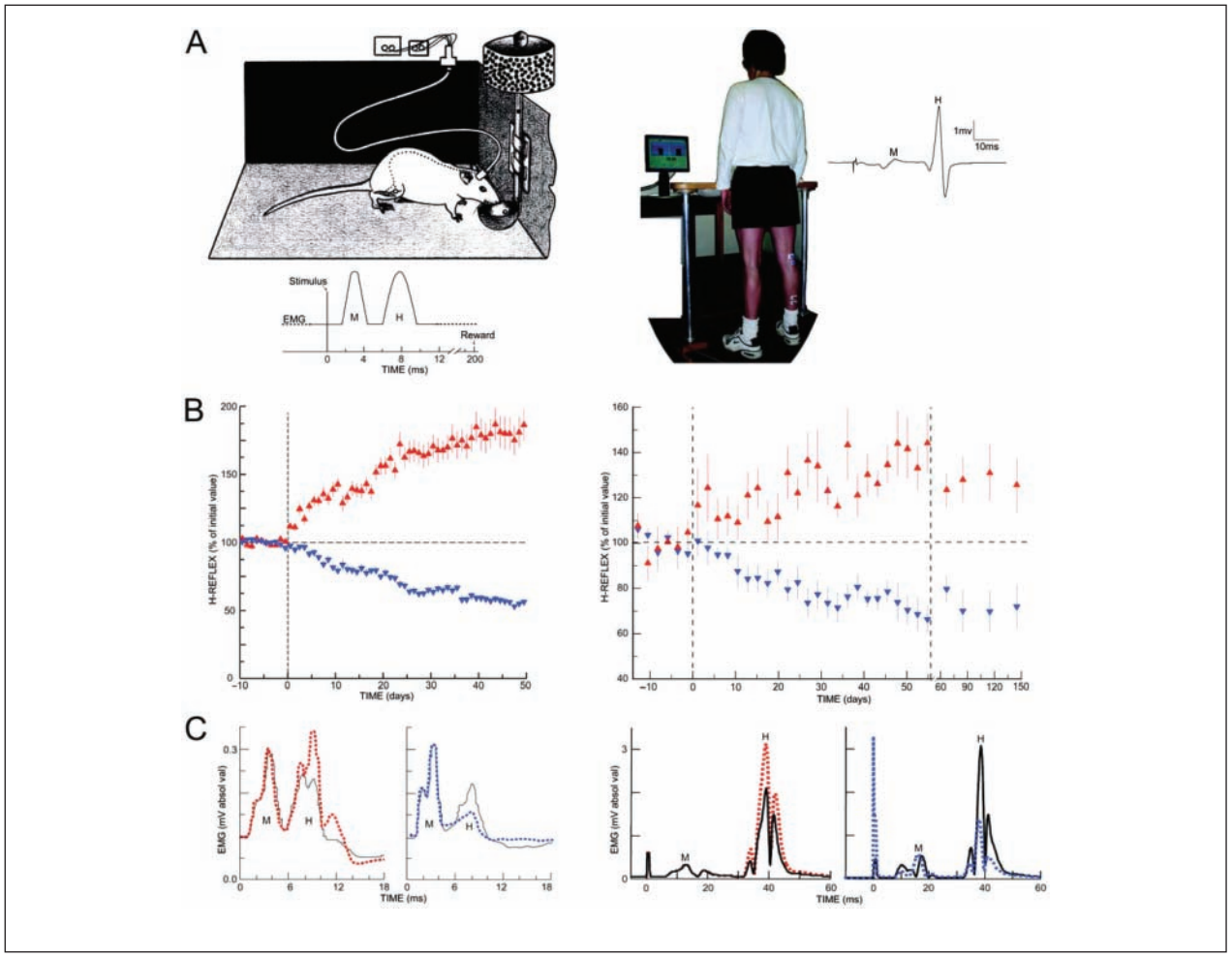

Figure 2. The reflex operant conditioning protocol and its results in rats and humans. (A) The conditioning protocol. Left: Soleus muscle activity is monitored 24 h/d in a rat with chronically implanted electromyography (EMG) electrodes and a tibial nerve cuff. The implant wires travel subcutaneously to a head-mounted connector and then through a flexible cable and a commutator to amplifiers and stimulator. The rat can move freely about the cage. Whenever the absolute (i.e., rectified) value of soleus EMG stays in a specified range for a randomly varying 2.3- to 2.7-second period, a nerve cuff stimulus elicits a threshold M-wave (i.e., a direct muscle response) and an H-reflex. The trace shows a single trial (with EMG displayed as absolute value). A rat averages 2000 to 6000 trials per day. From Wolpaw 1997. Right: Soleus activity is monitored in a person with EMG recording electrodes over the muscle and with nerve-stimulating electrodes in the popliteal fossa over the tibial nerve. The person maintains a standard erect posture facing a video screen that displays the current level (absolute value) of soleus EMG in relation to a specified range. Whenever the absolute value of soleus EMG stays in this range for several seconds, tibial nerve stimulation elicits a threshold M-wave and an H-reflex. The trace shows a single trial (with EMG displayed in traditional fashion as actual [i.e., unrectified] value). A person completes three 225-trial sessions per week. Modified from Thompson and others 2009. (B) The course of H-reflex change. Left: For the first 10 days (from day –10 to day 0), the rat is exposed to the control mode, in which no reward occurs and the H-reflex is simply measured to determine its initial size. For the next 50 days, it is exposed to the up-conditioning or down-conditioning mode, in which a food-pellet reward occurs whenever the H-reflex is above (HRup mode) or below (HRdown mode) a criterion value. The background EMG and the M-wave stay constant throughout. Successful conditioning (defined as a change of at least 20% in the correct direction) occurs in 75% to 80% of the rats (the others remain within 20% of their control value). The graphs show average (±SEM) daily H-reflex sizes for 55 successful HRup rats (red ▲) and 72 successful HRdown rats (blue ▼). In both groups, mode-appropriate change in H-reflex size develops steadily over the 50 days. If a rat is switched from the up mode to the down mode (or vice versa), the H-reflex change reverses in the same gradual fashion. Updated from Wolpaw 1997. Right: Each person completes 3 sessions per week. For the first 6 sessions (from day –14 to day 0), the person is exposed to the control mode, in which the H-reflex is simply measured to determine its initial size. For the next 24 sessions (days 0-56), the person is exposed to the HRup or HRdown conditioning mode, in which for each trial the video screen provides immediate feedback indicating whether the H-reflex is above (HRup mode) or below (HRdown mode) a criterion value. After completing these 24 conditioning sessions, people return for 4 follow-up sessions over the next 3 months. The background EMG and the M-wave stay constant throughout. Successful conditioning occurs in about 80% of the people. The graphs show average (±SEM) daily H-reflex sizes for 6 successful HRup people (red ▲) and 8 successful HRdown people (blue ▼). In both groups, mode-appropriate change in H-reflex size develops steadily over the 24 conditioning sessions. In the follow-up sessions, the H-reflex increase in the HRup group is smaller but still evident, and the H-reflex decrease in the HRdown group persists unchanged. From Thompson and others 2009. (C) Examples of H-reflex change. Left: Average poststimulus EMG (absolute value) for representative days from an HRup rat (left) and an HRdown rat (right) under the control mode (solid) and near the end of HRup or HRdown conditioning (dashed). The H-reflex is larger after up-conditioning and smaller after down-conditioning, while background EMG (shown here by EMG at time zero) and M-waves are not changed. From Wolpaw 1997. Right: Average poststimulus EMG (absolute value) for representative sessions from an HRup person (left) and an HRdown person (right) under the control mode (solid) and near the end of HRup or HRdown conditioning (dashed). The H-reflex is larger after up-conditioning and smaller after down-conditioning, while background EMG and M-waves are not changed. Stimulus artifacts are present at 0 milliseconds. From Thompson and others 2009.

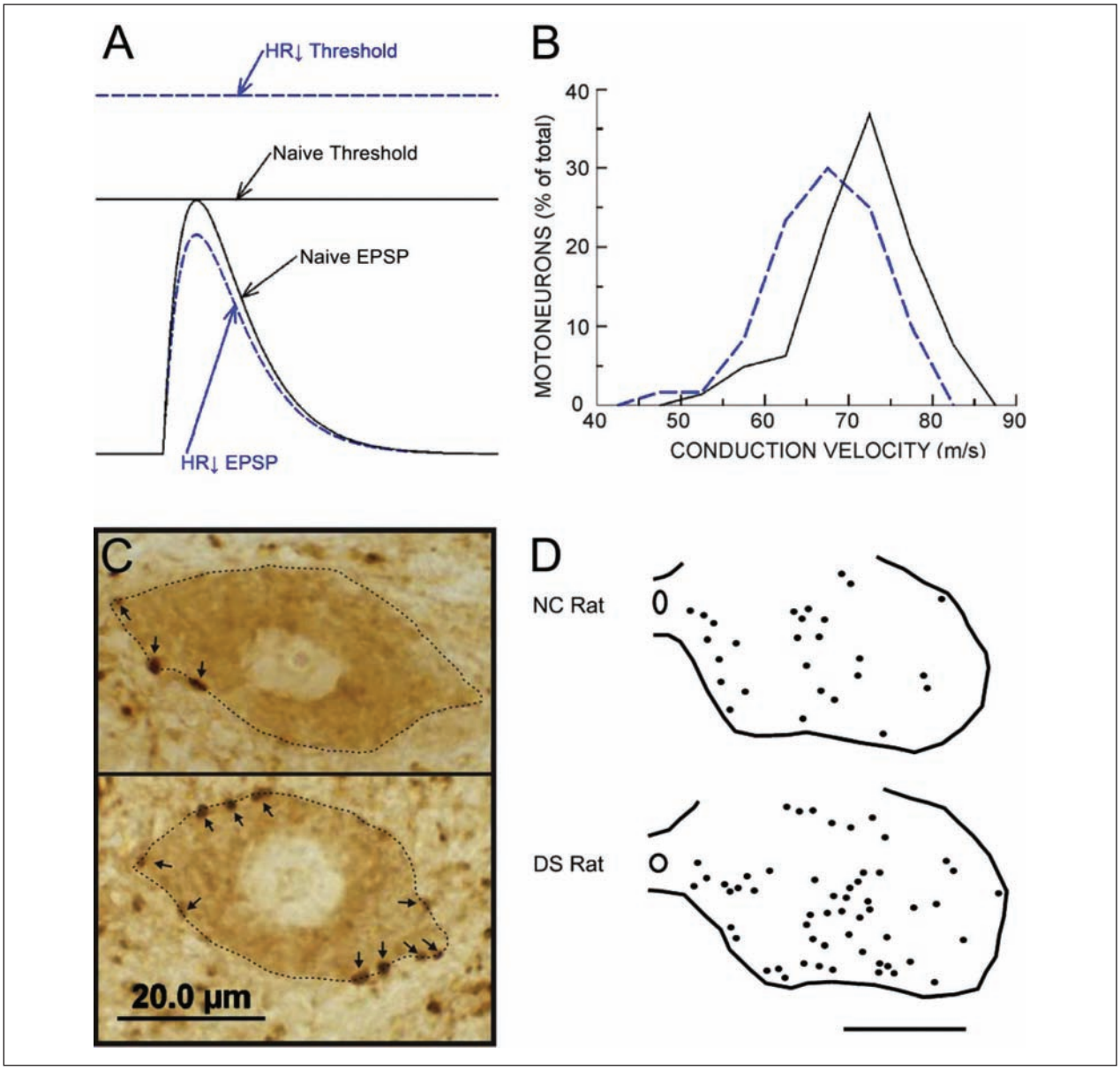

Figure 3. Examples of the multisite spinal cord plasticity that accompanies H-reflex conditioning. (A) Motoneurons in down-conditioned (HR↓) monkeys have more positive firing thresholds and slightly smaller primary afferent excitatory postsynaptic potentials (EPSPs). Together, these 2 findings can explain why the H-reflex is smaller. From Wolpaw 1997. (B) Distributions of soleus motoneuron axonal conduction velocities in unconditioned (solid) and down-conditioned (dashed) rats. Down-conditioning reduces conduction velocity in monkeys as well as in rats. The more positive motoneuron firing threshold (i.e., Fig. 3A) can account for the slower conduction velocity. From Wolpaw and Chen 2009. (C) Soleus motoneurons (dashed lines) from an unconditioned rat (top) and a down-conditioned rat (bottom). Arrows point to GABAergic terminals on the somatic membrane. The terminals are identified by glutamic acid decarboxylase (GAD_{67}) immunoreactivity. After down-conditioning, soleus motoneurons have more GABAergic terminals, and these terminals are more densely labeled and cover more of the somatic membrane. From Wang and others 2006. (D) Camera lucida drawings of ventral horn from lumbar 4 and 5 spinal cord sections from a control rat (NC) (top) and a successfully down-conditioned rat (DS) (bottom) showing GAD_{67}-positive interneurons (GAD-INs). Each drawing includes the GAD-INs from 2 adjacent 25-µm sections. The number of GAD-INs is clearly greater in the down-conditioned rat than in the control rat. Scale bar: 500 µm. From Wang and others 2009.

(Wang and others 2006, 2009). They are illustrated in Figure 3C and 3D. These GABAergic changes (as well as the changes in motoneuron threshold and conduction velocity) occur only in the 75% to 80% of animals in which conditioning is successful (i.e., the animals in which the H-reflex changes at least 20% in the correct direction).

They do not occur in the 20% to 25% of animals in which conditioning fails (i.e., the H-reflex remains within 20% of its initial value). This specificity suggests that these GABAergic changes contribute to the conditioned reflex change.

Down-conditioning and up-conditioning are not mirror images of each other but rather have different mechanisms. In contrast to the motoneuron plasticity that appears to be responsible for down-conditioning, up-conditioning probably results from a change in oligosynaptic primary afferent input to the motoneuron (Carp and Wolpaw 1995; Wolpaw and Chen 2001). The lower part of Figure 4 indicates the numerous sites of plasticity in the spinal cord ipsilateral to the conditioned soleus H-reflex. H-reflex conditioning also changes the other side of the spinal cord (Wolpaw and Lee 1989). This contralateral plasticity has yet to be explored.

Comparable Plasticity in Real Life

The spinal cord plasticity accompanying H-reflex conditioning is not simply a laboratory curiosity. Similar plasticity, driven by descending and peripheral inputs, shapes spinal cord function in development and continues to modify it throughout life. As an organism's behavioral repertoire changes and expands throughout life, this continual plasticity ensures that the spinal cord is always in a state able to accommodate all the behaviors in the current repertoire.

In early life, input from the brain guides the plasticity that eventually produces an adult spinal cord that supports standard motor skills like manipulation, exploration, and locomotion and can also support specialized skills like dancing or playing the piano. In this development process, descending inputs and concurrent peripheral inputs gradually establish normal patterns of spinal proprioceptive, flexion withdrawal, and autonomic reflexes (Wolpaw and Tennissen 2001; de Groat 2002; Wolpaw 2006). When perinatal trauma or disease (e.g., cerebral palsy) disrupts descending input, infantile reflex patterns may last into adulthood and contribute to disabilities. Figure 5A and 5B illustrate the impact of perinatal disruption of descending input on proprioceptive reflexes in humans and on flexion withdrawal reflexes in rats.

The learning of new skills later in life is accompanied by changes in spinal cord reflexes similar to those produced in the laboratory (Wolpaw and Tennissen 2001; Wolpaw 2006, for review). Reflexes are affected by the nature, intensity, and duration of physical activity and by particular training programs. Stretch reflexes and H-reflexes are different in athletes versus nonathletes and across different types of athletes. These differences are thought to

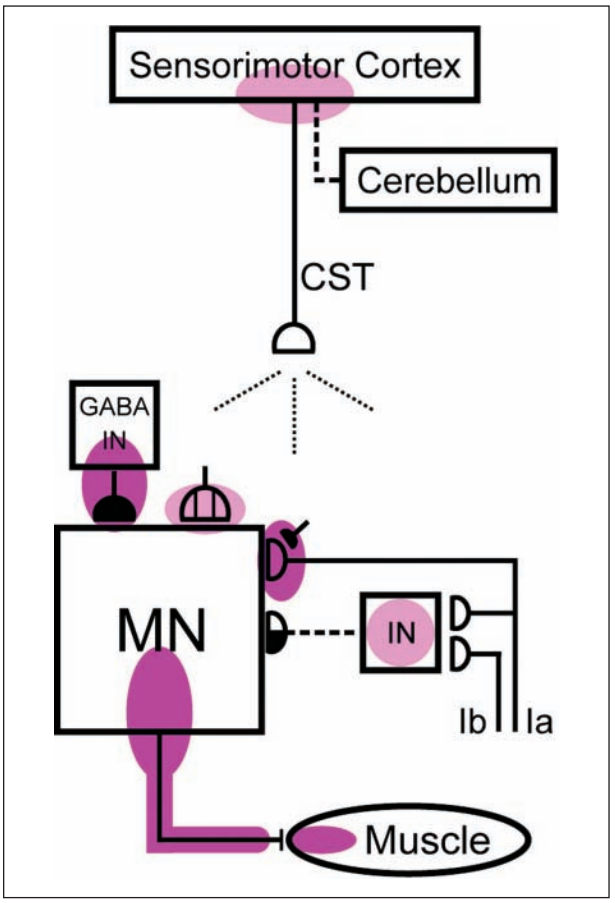

Figure 4. A hierarchy of brain and spinal cord plasticity underlies H-reflex conditioning. The shaded ovals indicate the spinal and supraspinal sites of the plasticity associated with operant conditioning of the spinal stretch reflex (SSR) or its electrical analog, the H-reflex. "MN" is the motoneuron, "CST" is the main corticospinal tract, "IN" is a spinal interneuron, and "GABA IN" is a GABAergic spinal interneuron. 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. The monosynaptic and probably oligosynaptic SSR/H-reflex pathway from Ia and Ib afferents to the motoneuron is shown. Definite (purple shading) or probable (pink shading) sites of plasticity include the motoneuron membrane (i.e., firing threshold and axonal conduction velocity), motor unit properties, GABAergic interneurons, GABAergic inhibitory terminals and C terminals on the motoneuron, the Ia afferent synaptic connection, terminals conveying disynaptic group I inhibition or excitation to the motoneuron, and sensorimotor cortex. The essential roles of the corticospinal tract (which originates largely in sensorimotor cortex) and of cerebellar output to cortex are indicated. The spinal plasticity that is directly responsible for H-reflex conditioning appears to be induced and maintained by cortical plasticity that itself depends for its long-term survival on the cerebellum (see text). Modified and updated from Wolpaw and Tennissen 2001. See Wolpaw 2006 for review.

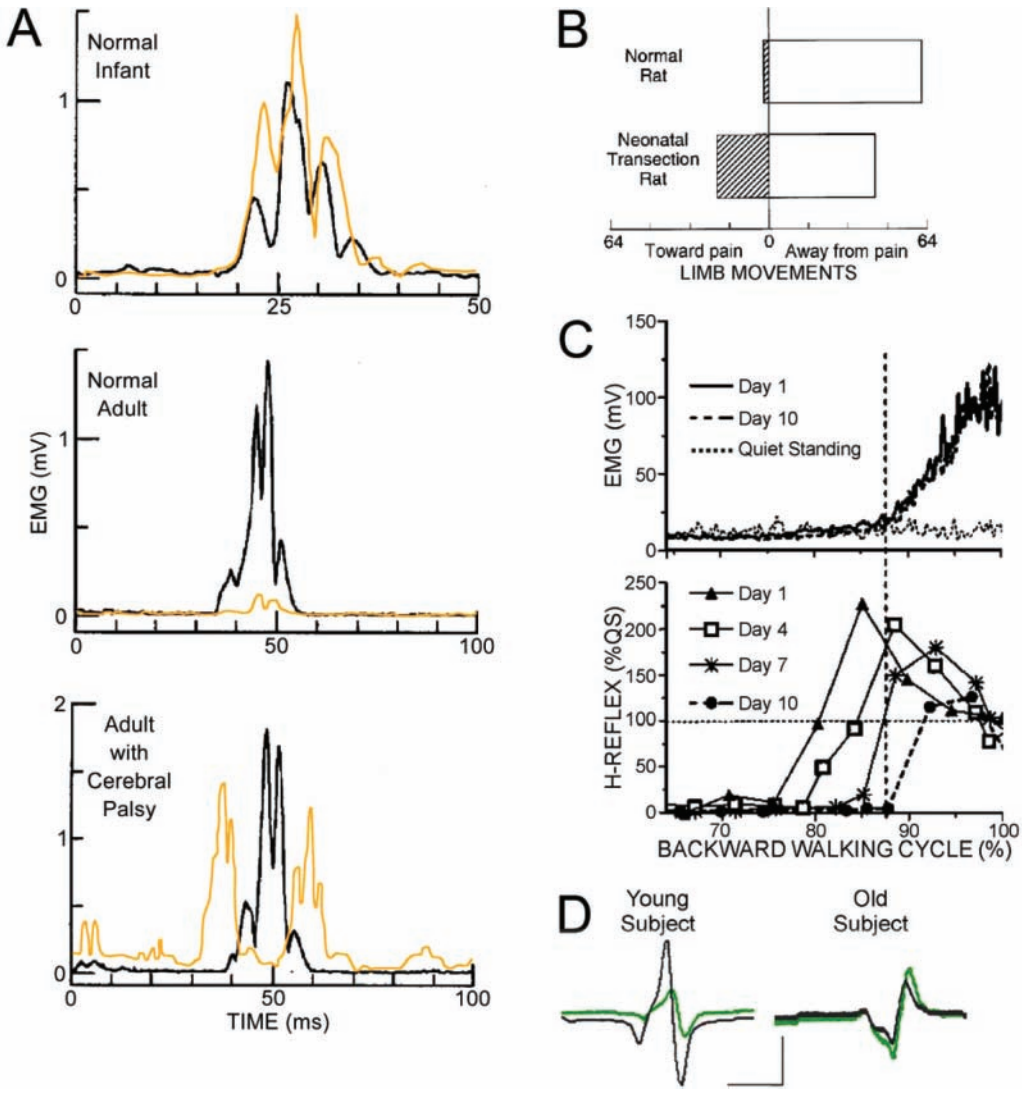

Figure 5. Spinal cord reflexes change throughout life. (A) Short-latency electromyographic (EMG) responses from soleus (black) and tibialis anterior (orange) muscles to sudden foot dorsiflexion, which stretches the soleus and shortens the tibialis anterior, in a normal infant, a normal adult, and an adult with cerebral palsy. In the normal infant, spinal stretch reflexes occur in both muscles. In the normal adult, a reflex occurs only in the muscle that is stretched, that is, the soleus, while little or no response occurs in the tibialis anterior. However, in the adult with cerebral palsy, in whom perinatal supraspinal injury has impaired descending influence, the infantile pattern has not disappeared, and reflexes occur in both muscles. From B. Myklebust, unpublished data; see Myklebust and others 1982, 1986 for comparable data. (B) The direction of flexion withdrawal responses to painful stimuli in normal adult rats and in adult rats in which the spinal cord was transected just after birth. In normal adults, the direction of the response is almost always appropriate (i.e., the limb moves away from the painful stimulus), while in transected adults, it is often inappropriate (i.e., the limb moves toward the stimulus). Neonatal spinal cord transection abolishes the descending input that gradually shapes normal (i.e., appropriate) flexion withdrawal responses. Modified from Levinsson and others 1999. (C) Modulation of soleus H-reflex size as a function of time in the step cycle as a person masters backward walking over 10 days. Top: Soleus EMG activity on day 1 (solid line) and day 10 (dashed line) just before and after onset of the soleus burst that occurs in the stance phase of the cycle. Soleus EMG is the same on days 1 and 10. The dotted line indicates soleus EMG during quiet standing. Bottom: H-reflex size (as percentage of size during quiet standing) versus time in the backward-walking step cycle for days 1, 4, 7, and 10 of training. Soleus EMG does not change with training. In contrast, the marked increase in H-reflex size before the soleus burst that is seen on day 1 disappears by day 10. Modified from Schneider and Capaday 2003. (D) Soleus H-reflexes of a younger person and an older person in prone (gray) and standing (green) positions. In older subjects, the H-reflex is usually smaller and less affected by body position. Modified from Koceja and others 1995.

contribute to the distinctive skills of these different groups. For example, H-reflexes and disynaptic reciprocal inhibition are very small in the leg muscles of professional ballet dancers (Nielsen and others 1993). The diminished peripheral influence on motoneurons represented by these smaller reflexes is likely to increase cortical control and enable muscle coactivation and may thereby facilitate the high precision and specialized actions essential in this form of dance. More limited, sharply focused training programs provide further evidence for activity-dependent plasticity in spinal cord reflexes (e.g., Schneider and Capaday 2003; Meunier and others 2007), as do the reflex changes associated with aging (e.g., Koceja and others 1995) (Fig. 5C and 5D).

The Role of the Brain in Reflex Conditioning

In the laboratory protocol (Fig. 2A), the imposition of the reward contingency (i.e., reward for a larger or smaller H-reflex) operantly conditions the brain to produce descending activity that changes the H-reflex appropriately. As descending activity varies over its normal spontaneous range, the reward contingency ensures that activity that increases reward probability is rewarded, while activity that decreases it is not. The result is that descending activity shifts so as to increase reward probability. Current understanding is that the initial development of this shift produces the rapid phase 1 change in H-reflex size and that its long-term persistence induces the progressive spinal cord plasticity responsible for gradual phase 2 H-reflex change (Wolpaw and O'Keefe 1984; Thompson and others 2009). The first question raised by this descending activity is the identity of the pathway(s) that convey it. The task of answering this question was greatly facilitated by one of the principal advantages of a spinal cord model—that the spinal cord is connected to the brain by well-defined pathways accessible to interruption.

A series of pathway transection studies clearly answered the question of which pathway(s) convey the descending activity that changes the H-reflex. Of the major descending and ascending tracts, only the corticospinal tract (CST) is essential (Chen and Wolpaw 2002; Chen XY and others 2002, 2006). CST transection or ablation of its site of origin, the contralateral sensorimotor cortex, prevents H-reflex conditioning, while transection of other major descending tracts or of the dorsal column ascending tract does not do so. Furthermore, if the CST is cut in rats in which the H-reflex has already been reduced by down-conditioning, the reflex decrease disappears over 5 to 10 days, and the H-reflex actually becomes significantly larger than it was prior to down-conditioning. Figure 6 illustrates this finding. The spinal cord plasticity that is responsible for the smaller H-reflex can survive for only a few days on its own. Because the CST is not thought to contact motoneurons in rat lumbar spinal cord (Wang and others 2009, for review), the critical CST influence is probably conveyed to the motoneurons by spinal interneurons. At present, GABAergic interneurons in spinal laminae 6 and 7 are the best candidates (Wang and others 2006, 2009) (Fig. 3D).

Down-conditioning also depends on the cerebellum: it does not occur in rats in which the cerebellar output nuclei dentate and interpositus have been ablated (Chen and Wolpaw 2005). This cerebellar contribution consists of cerebellar output to cortex rather than to spinal cord because transection of the lateral column (which contains the rubrospinal tract, the principal cerebellar-spinal connection) does not prevent conditioning. The cerebellum is also essential for long-term maintenance of this learning: if the cerebellar output nuclei are ablated after the H-reflex has already been reduced by down-conditioning, the reflex decrease lasts for 40 days and then disappears over the next 10 days (Wolpaw and Chen 2006). This surprising finding implies that the CST activity that maintains the spinal cord plasticity responsible for the H-reflex decrease depends on supraspinal plasticity that can survive for 40 days without cerebellar influence. Forty days after cerebellar influence is removed, this supraspinal plasticity apparently disintegrates, and the H-reflex becomes even larger than it was prior to down-conditioning.

A Hierarchy of Plasticity

Figure 4 summarizes the present understanding of the complex multisite plasticity that is associated with H-reflex conditioning. The transection and ablation studies summarized in the previous section suggest that the changes in the spinal cord and in the brain comprise a hierarchy of plasticity: they imply that the reward contingency induces and maintains plasticity in the brain that produces the CST activity that induces and maintains the spinal cord plasticity that directly underlies the learned behavior (e.g., a smaller H-reflex). The existence of this hierarchy is revealed by the effects of the different lesions. The brain plasticity responsible for the CST activity that changes the spinal cord survives 40 days after loss of cerebellar influence, and the spinal cord plasticity directly responsible for the smaller H-reflex survives only 5 to 10 days after CST transection. This simple learning is acquired and maintained through a hierarchy of plasticity in the brain and the spinal cord.

Multisite Plasticity Is Necessary and Inevitable

As Figure 4 summarizes, H-reflex conditioning produces many changes in the spinal cord. The number of these

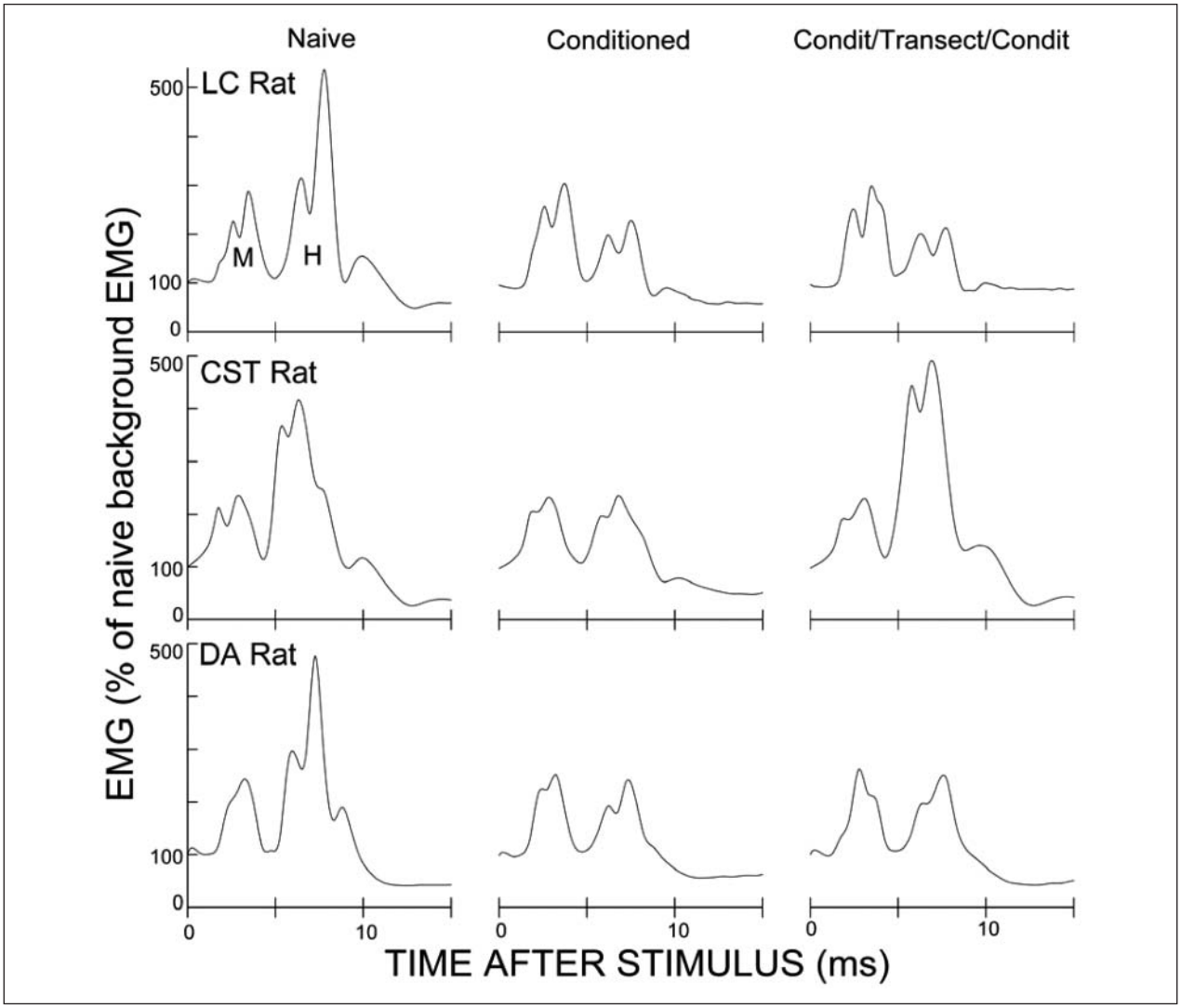

Figure 6. The corticospinal tract (CST) is essential for maintenance of H-reflex down-conditioning. Average poststimulus electromyography (EMG) from 3 rats for representative days: (left) before down-conditioning; (center) at the end of down-conditioning and before midthoracic transection of the right lateral column (LC rat), the corticospinal tract (CST rat), or the dorsal ascending tract (DA rat); and (right) after transection and continued down-conditioning. All 3 rats decreased the H-reflex (H) in response to down-conditioning. LC or DA transection did not affect the decrease. In contrast, CST transection abolished the decrease in 5 to 10 days and led to an H-reflex larger than the original, control-mode H-reflex. Background EMG (indicated by the EMG at time zero) and M-wave (M) did not change over the course of study. From Chen and Wolpaw 2002.

changes is almost certain to grow further as exploration expands beyond the relatively limited studies to date. Some elements of this complex plasticity appear to underlie the learned change in the H-reflex. Thus, the positive shift in motoneuron threshold explains why down-conditioning makes the H-reflex smaller. However, other elements, like the contralateral plasticity, seem to be unrelated to the modified H-reflex that is the goal of the conditioning protocol. Nevertheless, these seemingly inexplicable changes may be both necessary and inevitable.

The spinal cord neurons and synapses changed by H-reflex conditioning serve many other behaviors, such as locomotion. Thus, the plasticity responsible for H-reflex change (e.g., a positive shift in motoneuron firing threshold), which might be labeled *primary* plasticity, is likely to affect other behaviors as well. As a result, *compensatory* plasticity may be necessary to protect these other behaviors from the disruptive impact of the plasticity responsible for the H-reflex change. For example, the afferent input that excites the soleus H-reflex also contributes

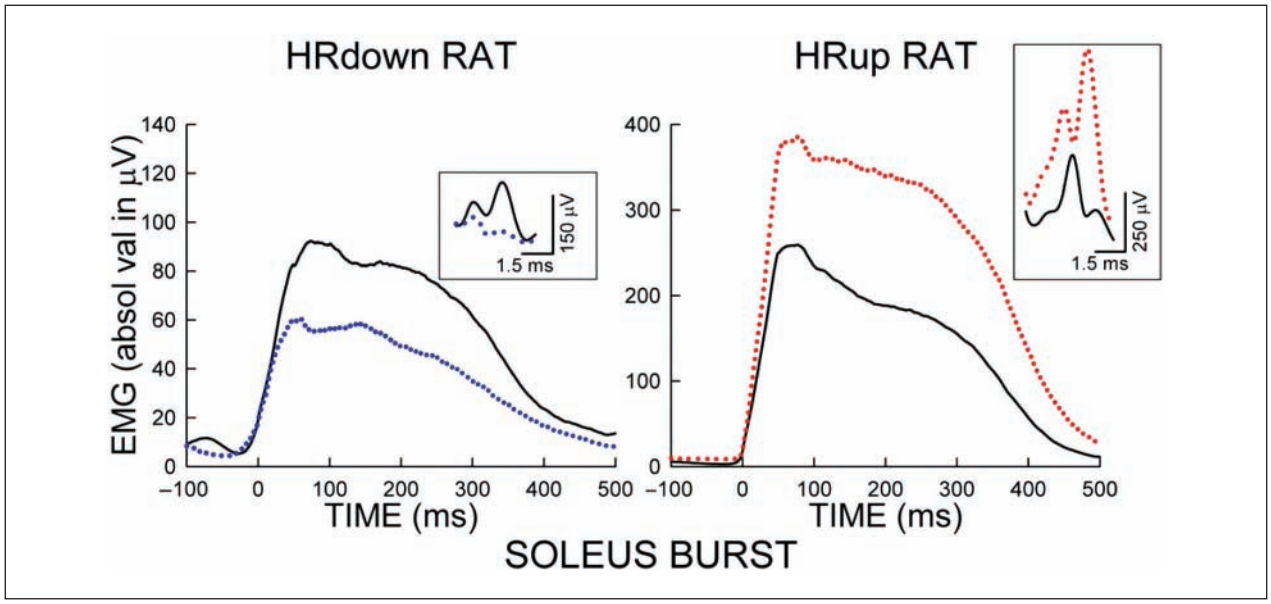

Figure 7. Spinal reflex conditioning affects muscle activity during locomotion. Average right soleus locomotor bursts before (solid) and after (dotted) H-reflex conditioning from a down-conditioned (HRdown) and an up-conditioned (HRup) rat. The insets show the average right soleus H-reflexes measured in the stance phase of locomotion before (solid) and after (dotted) conditioning. After conditioning, both the stance H-reflex and the soleus burst are smaller in the down-conditioned rat and larger in the up-conditioned rat. Primary afferent excitation contributes to the locomotor burst. Thus, the changes in the strength of this excitation that are caused by H-reflex conditioning affect the size of the burst. Modified from Chen and others 2005.

to the burst of soleus activity that supports the stance phase of locomotion (Yang and others 1991; Bennett and others 1996; Stein and others 2000). As a result, when H-reflex up-conditioning or down-conditioning changes H-reflex size, it also changes the soleus locomotor bursts: the burst tends to be larger after up-conditioning and smaller after down-conditioning (Chen and others 2005). Figure 7 illustrates this effect. Recent studies suggest that compensatory changes in the reflex pathways serving other leg muscles may prevent this change in the soleus burst from causing the animal to limp (i.e., to have an asymmetrical gait) (Chen L and others 2009; Chen Y and others 2009).

Furthermore, because activity-dependent plasticity is ubiquitous in the CNS, primary and compensatory plasticity, simply by changing ongoing activity, are likely to induce additional, *reactive* (or downstream) plasticity. Reactive plasticity is distinguished by the fact that its origin is entirely within the CNS and generally very local. Whereas primary and compensatory plasticity are driven by the consequences of behavior, reactive plasticity reflects the impact of local changes in activity on individual neurons or synapses. That is, primary and compensatory plasticity depend on what happens in the outside world, while reactive plasticity does not; its origin is entirely internal. For example, an increase in the number of action potentials reaching a synapse may reduce the size of the excitatory postsynaptic potential (EPSP) that each one produces in the postsynaptic neuron (e.g., Arai and Lynch 1998). Such desensitization is an instance of reactive plasticity: its mechanism is entirely local, and it occurs regardless of any effect it has or does not have on behavior.

In sum, even learning as ostensibly simple as a larger or smaller H-reflex is necessarily and inevitably associated with a complex pattern of plasticity that extends well beyond the changes responsible for the modified H-reflex (Wolpaw and Lee 1989; Wolpaw and Tennissen 2001). This unavoidable complexity is probably the single most important reason learning and memory need to be studied in the simplest and most accessible models.

A Negotiated Equilibrium

As noted previously, the spinal cord generally and its motoneurons specifically are the final common pathway for essentially all learned behaviors. These behaviors share the same common substrate of spinal neurons and synapses. In a normal CNS, the brain maintains these spinal cord elements in a state that satisfactorily serves the disparate needs of the many different behaviors in the organism's repertoire. For example, the strengths of proprioceptive reflex pathways are kept in ranges that accommodate the

requirements of walking as well as running, and flexion withdrawal reflex pathways are maintained so as to ensure sharply focused responses to painful inputs. The importance of this long-term maintenance is indicated most graphically by the profound abnormalities that follow disruption of the brain's influence by injury or disease.

New learning experiences add new behaviors to the repertoire. For many experiences (e.g., learning to walk, ballet training, backward walking, H-reflex conditioning), this process includes modifications in the brain's ongoing influence over spinal pathways. This altered influence adjusts spinal cord pathways to accommodate the new behavior and maintains them in this new state. Thus, as noted above for H-reflex conditioning, such behaviors depend on hierarchies in which supraspinal plasticity induces and maintains spinal cord plasticity appropriate to the behaviors. The picture that emerges is of a spinal cord in a state of equilibrium that reflects and accommodates the competing demands of many different learned behaviors. As each newly learned behavior adds the primary plasticity that produces it, this plasticity combines with concurrent compensatory and reactive plasticity in both brain and spinal cord to establish a new spinal cord equilibrium that accommodates the needs of the expanded repertoire. The state of the spinal cord reflects continual negotiation among the hierarchies responsible for many different behaviors; it is essentially a negotiated equilibrium.

The Importance of Spinal Cord Plasticity

It seems clear that activity-dependent spinal cord plasticity has a key role in learned behaviors that require finely tuned muscle contractions combined with precise responses to concurrent sensory inputs. These range from standard behaviors such as walking and talking to more specialized athletic and artistic skills. Such behaviors depend on plasticity distributed throughout the CNS, from cortex to spinal cord. Defining the spinal cord's role is an essential part of explaining such behaviors. Furthermore, the spinal cord, given its immediate proximity to behavior as well as its relative simplicity, experimental accessibility, and distance from the brain, is a logical and convenient place to start defining exactly how learning changes behavior. Spinal cord plasticity connects directly to behavior, while plasticity elsewhere can affect behavior only through other areas, which themselves may change.

Spinal cord plasticity also has substantial clinical significance. Disorders such as stroke and spinal cord injury distort spinal circuitry and impair behaviors, such as locomotion and micturition, that depend heavily on this circuitry. Thus, methods for inducing and guiding spinal cord plasticity could help to restore useful motor function. Recent studies indicate the clinical promise of reflex conditioning for restoring function after spinal cord injury (Chen Y and others 2006). In rats, midthoracic transection of the right lateral column produces asymmetrical walking due to weak right stance. As Figure 8 illustrates, up-conditioning the right soleus H-reflex strengthens the right soleus burst and eliminates this asymmetry. Efforts have begun to determine whether reflex conditioning protocols can also improve function in people with partial spinal cord injuries (Pomerantz and others 2009). Such protocols could be particularly valuable when spinal cord regeneration becomes possible and techniques for re-educating the newly regenerated spinal cord become essential in order to restore useful function (Wolpaw 2006).

The Wider Value of Spinal Cord Models

Spinal cord plasticity is important in developing and maintaining motor skills such as those mentioned in the last section, and spinal cord models are certainly important for exploring this plasticity. But do spinal cord plasticity and spinal cord models have wider importance? The learning and memory phenomena that usually draw the most interest are those that occur quickly, such as memorizing a list of words in a few minutes or the route to a new location after one repetition. This interest is exemplified by the focus on rapid synaptic phenomena such as the various forms of LTP. Plasticity that develops gradually, plasticity like that prominent in the spinal cord, has traditionally drawn less interest. Furthermore, many (perhaps most) learning and memory phenomena are not likely to involve spinal cord plasticity. Learning the multiplication tables, the names of new acquaintances, or the distinctive styles of different Renaissance painters probably does not depend on changes in spinal cord pathways. Nevertheless, gradual plasticity like that found in the spinal cord is likely to be a prerequisite for most learning, and spinal cord models can identify principles and elucidate problems that apply to learning and memory in general.

The many kinds of rapid learning that are prominent in normal life and that dominate laboratory studies are not self-contained or de novo phenomena that occur in isolation; rather, they are critically dependent on skills that are acquired gradually through practice. Just as locomotion and effective flexion withdrawal are skills acquired gradually during early life, the ability to quickly learn a new word, a new set of directions, a new face, or a new equation rests on language, orientation, facial recognition, or mathematical skill that is also acquired gradually through practice. In the absence of such practice, without the framework of activity-dependent plasticity that prolonged practice gradually produces, these examples of rapid learning

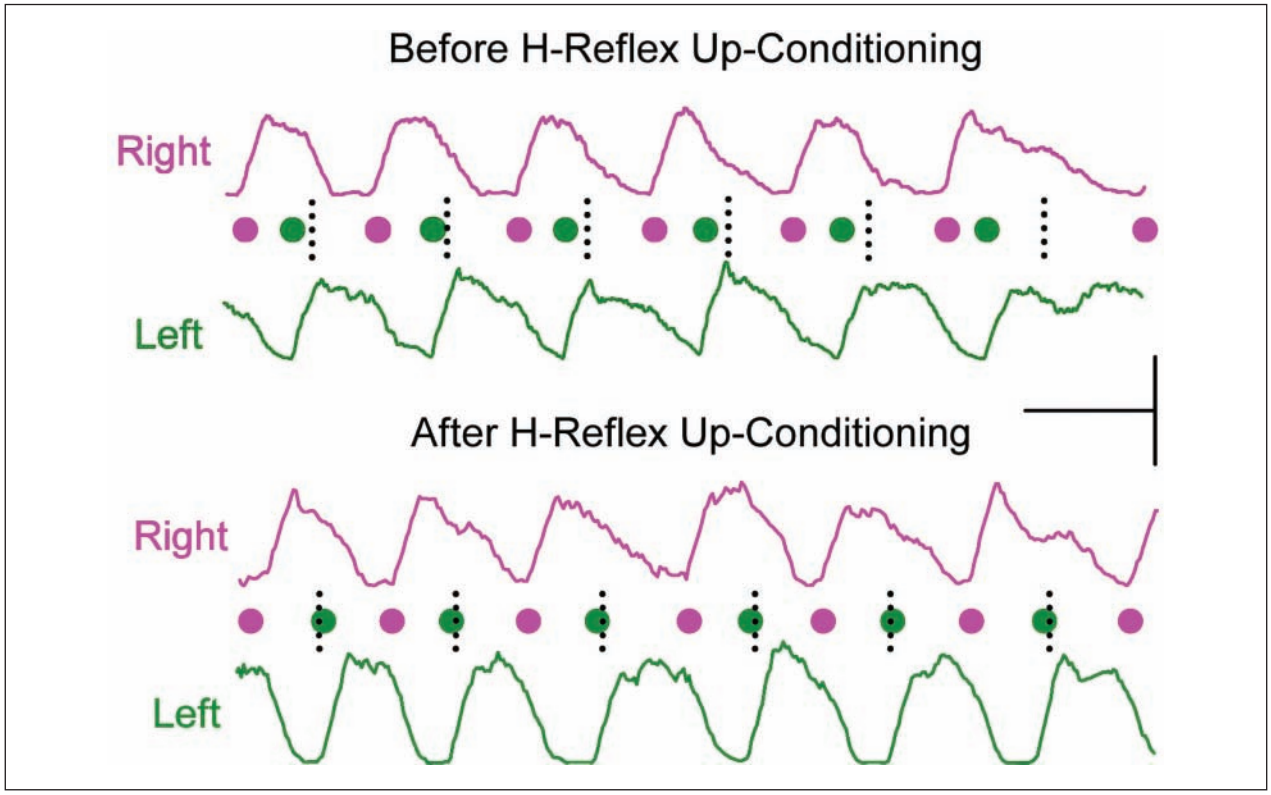

Figure 8. H-reflex conditioning can improve walking after spinal cord injury. The traces show the bursts of rectified electromyographic (EMG) activity from right and left soleus muscles during treadmill locomotion before (top) and after (bottom) up-conditioning has increased the right soleus H-reflex in a rat with a right lateral-column (LC) transection. The onsets of the right and left stance phases of the step cycle are marked by the violet and green circles, respectively. The short vertical dashed lines indicate the midpoints between right burst onsets, which is where the left burst onsets should occur. Before up-conditioning, the left burst onset occurs too early, and the gait is asymmetrical. After up-conditioning has strengthened the right soleus burst, the left burst onset occurs at the correct time, and the asymmetry is gone. Horizontal scale bar: 0.5 seconds; vertical scale bar: 100 and 150 μV for the right and left bursts, respectively. From Chen Y and others 2006.

would not be possible. People can learn lists of words in their own languages quickly (while they learn nonsense syllables much more slowly [Davis 1930; Jenkins 1985]), but these languages took many months or years of training to master. A person can readily distinguish different faces and can easily learn to recognize a new acquaintance, but the gradual acquisition of that ability occupies much of the first year of life (Nelson 2001).

In a broader context, it seems that rapid learning phenomena generally represent relatively minor adjustments or additions to complex frameworks of plasticity that developed gradually over prolonged periods. Certainly, the mechanisms responsible for these rapid events are important in themselves and may exert long-term effects on the framework itself. Nevertheless, effective exploration of learning and memory requires, and logically begins with, study of the gradual long-term plasticity that is a prerequisite for most learning and memory. Only when the complex patterns of plasticity produced by practice are understood will it be possible to fully explain how most rapid learning phenomena are actually produced. And, as the previous sections illustrate, the spinal cord can provide models that are uniquely advantageous for exploring the gradual activity-dependent plasticity responsible for skill acquisition and maintenance. The spinal cord's distinctive features—simplicity, accessibility, anatomical separation, and direct connection to behavior—compel the recognition and facilitate the study of primary, compensatory, and reactive plasticity. For example, the impact of H-reflex conditioning on locomotion can be directly connected to changes in specific spinal pathways (Chen Y and others 2005, 2006) (Figs. 7 and 8). Thus, it should be possible through straightforward studies to determine exactly how normal gait is preserved in spite of the primary plasticity responsible for H-reflex conditioning. Furthermore, the distinctive features of the spinal cord make it possible to

recognize the existence of hierarchies of plasticity and to formulate the associated concept of the state of the spinal cord as a negotiated equilibrium.

Perhaps most important, the principles that emerge from spinal cord models are likely to apply also to learning that involves less accessible areas. Numerous studies have documented the changes that experience produces in sensory and motor cortical areas and have shown that this plasticity is accompanied by subcortical changes as well (Jones 2000; Matsuura and others 2002; Froemke and others 2007; Kaas and others 2008; Chakrabarty and others 2009). While the spinal cord, as the final common pathway for all behavior, is the foremost example of a multitask CNS structure, these cortical areas also support a continually changing repertoire of many different behaviors. Therefore, they too may be expected to display primary, compensatory, and reactive plasticity, to participate in hierarchies in which plasticity in one area induces and maintains plasticity in another, and to exist in states of negotiated equilibria that accommodate the disparate needs of many different learned behaviors.

Thus, the fact that spinal cord plasticity is a component of many motor skills is only one aspect, and probably not the most important aspect, of its significance for understanding learning and memory. Spinal cord models facilitate the recognition and exploration of principles that are likely to apply to learning throughout the CNS.

Conclusion

The recognition that many kinds of activity-dependent plasticity occur continually throughout the CNS and throughout life has transformed the challenge of explaining learning and memory into the problem of connecting this complex plasticity to behavior. The spinal cord and spinal cord plasticity are central to this endeavor for 2 reasons. First, the spinal cord is the final common pathway for all behavior, and spinal cord plasticity has a part in the acquisition and maintenance of many motor skills. Second, by virtue of its simplicity, accessibility, separation from the brain, and closeness to behavior, the spinal cord is uniquely suited for studying how activity-dependent plasticity (particularly gradual plasticity) explains behavior and for identifying principles and concepts that apply to learning throughout the CNS. Thus, the short answer to the question posed in the title "What can the spinal cord teach us about learning and memory?" is "A lot!"

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References

Adkins DL, Boychuk J, Remple MS, Kleim JA. 2006. Motor training induces experience-specific patterns of plasticity across motor cortex and spinal cord. J Appl Physiol 101: 1776–82.

Arai A, Lynch G. 1998. AMPA receptor desensitization modulates synaptic responses induced by repetitive afferent stimulation in hippocampal slices. Brain Res 799:235–42.

Bakkum DJ, Chao ZC, Potter SM. 2008. Long-term activity-dependent plasticity of action potential propagation delay and amplitude in cortical networks. PLoS One 3:e2088.

Balakrishnan S, Bellamy TC. 2009. Depression of parallel and climbing fiber transmission to Bergmann glia is input specific and correlates with increased precision of synaptic transmission. Glia 57:393–401.

Baldissera F, Hultborn H, Illert M. 1981. Integration in spinal neuronal systems. In: Brooks VB, editor. Handbook of physiology. Section I: the nervous system. Volume II: motor control, part I. Baltimore: Williams and Wilkins Company. p 509–95.

Bellamy TG, Ogden D. 2006. Long-term depression of neuron to glial signalling in rat cerebellar cortex. Eur J Neurosci 23:581–6.

Bennett DJ, De Serres SJ, Stein RB. 1996. Gain of the triceps surae stretch reflex in decerebrate and spinal cats during postural and locomotor activities. J Physiol 496:837–50.

Blazquez PM, Hirata Y, Highstein SM. 2004. The vestibule-ocular reflex as a model system for motor learning: what is the role of the cerebellum? Cerebellum 3:188–92.

Bramham CR. 2008. Local protein synthesis, actin dynamics, and LTP consolidation. Curr Opin Neurobiol 18:524–31.

Broussard DM, Kassardjian CD. 2004. Learning in a simple motor system. Learn Mem 11:127–36.

Brown WF. 1984. The physiological and technical basis of electromyography. Boston, MA: Butterworths.

Bruel-Jungerman E, Davis S, Laroche S. 2007a. Brain plasticity mechanisms and memory: a party of four. Neuroscientist 13:492–505.

Bruel-Jungerman E, Rampon C, Laroche S. 2007b. Adult hippocampal neurogenesis, synaptic plasticity and memory: facts and hypotheses. Rev Neurosci 18:93–114.

Butz M, Wörgötter F, van Ooyen A. 2009. Activity-dependent structural plasticity. Brain Res Rev 60:287–305.

Cantrell AR, Catterall WA. 2001. Neuromodulation of Na+ channels: an unexpected form of cellular plasticity. Nat Rev Neurosci 2:397–407.

Carp JS, Chen XY, Sheikh H, Wolpaw JR. 2001. Operant conditioning of rat H-reflex affects motoneuron axonal conduction velocity. Exp Brain Res 136:269–73.

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, Tennissen AM, Chen XY, Wolpaw JR. 2006. H-reflex operant conditioning in mice. J Neurophysiol 96:1718–27.

Carr DB, Day M, Cantrell AR, Held J, Scheuer T, Catterwall WA, and others. 2003. Transmitter modulation of slow, activity-dependent alterations in sodium channel availability endows neurons with a novel form of cellular plasticity. Neuron 39: 793–806.

Chakrabarty S, Friel KM, Martin JH. 2009. Activity dependent plasticity improves M1 motor representation and corticospinal tract connectivity. J Neurophysiol 101:1283–93.

Chen J, Yamahachi H, Gilbert CD. 2010. Experience-dependent gene expression in adult visual cortex. Cereb Cortex 20:650–60.

Chen L, Chen XY, Chen Y, Liu RL, Wang Y, Wolpaw JR. 2009. Conditioning of soleus H-reflex is accompanied by an opposite change in vastus lateralis H-reflex in freely moving rats. Program no. 79.1. Washington, DC: Society for Neuroscience Online.

Chen XY, Carp JS, Chen L, Wolpaw JR. 2002. Corticospinal tract transection prevents operantly conditioned increase of H-reflex in rats. Exp Brain Res 144:88–94.

Chen XY, Carp JS, Chen L, Wolpaw JR. 2006. Sensorimotor cortex ablation prevents H-reflex up-conditioning and causes a paradoxical response to down-conditioning in rats. J Neurophysiol 96:119–27.

Chen XY, Chen L, Wolpaw JR. 2001. Time course of H-reflex conditioning in the rat. Neurosci Lett 302:85–8.

Chen XY, Wolpaw JR. 1995. Operant conditioning of H-reflex in freely moving rats. J Neurophysiol 73:411–5.

Chen XY, Wolpaw JR. 2002. Probable corticospinal tract control of spinal cord plasticity in rats. J Neurophysiol 87: 645–52.

Chen XY, Wolpaw JR. 2005. Ablation of cerebellar nuclei prevents H-reflex down-conditioning in rats. Learn Mem 12: 248–54.

Chen Y, Chen XY, Jakeman LB, Schalk G, Stokes BT, Wolpaw JR. 2005. The interaction of a new motor skill and an old one: H-reflex conditioning and locomotion in rats. J Neurosci 25:6898–906.

Chen Y, Chen XY, Jakeman LB, Chen L, Stokes BT, Wolpaw JR. 2006. Operant conditioning of H-reflex can correct a locomotor abnormality after spinal cord injury in rats. J Neurosci 26:12537–43.

Chen Y, Chen L, Liu RL, Wang Y, Wolpaw JR, Chen XY. 2009. Soleus H-reflex conditioning may change locomotor EMG and kinematics. Program no. 79.2. Washington, DC: Society for Neuroscience Online.

Chen Y, Ghosh A. 2005. Regulation of dendritic development by neuronal activity. J Neurobiol 64:4–10.

Clarke E, O'Malley CD. 1996. The human brain and spinal cord. San Francisco: Norman Publishing.

Cohen JE, Fields RD. 2008. Activity-dependent neuron-glial signaling by ATP and leukemia-inhibitory factor promotes hippocampal glial cell development. Neuron Glia Biol 4: 43–55.

Compact Oxford English dictionary, second edition. 1993. Oxford, UK: Oxford University Press.

Courtine G, Gerasimenko Y, van den Brand R, Yew A, Musienko P, Zhong H, and others. 2009. Transformation of nonfunctional spinal circuits into functional states after the loss of brain input. Nat Neurosci 12:1333–42.

Croll RP. 2003. Complexities of a simple system: new lessons, old challenges and peripheral questions for the gill withdrawal reflex of Aplysia. Brain Res Rev 43:266–74.

Davis FC. 1930. The relative reliability of words and nonsense syllables as learning material. J Exp Psych 8:221–34.

de Groat WC. 2002. Plasticity of bladder reflex pathways during postnatal development. Physiol Behav 77:689–92.

Delgado-Garcia JM, Gruart A. 2006. Building new motor responses: eyelid conditioning revisited. Trends Neurosci 29:330–8.

Destexhe A, Marder E. 2004. Plasticity in single neuron and circuit computations. Nature 431:789–95.

De Zeeuw CI, Yeo CH. 2005. Time and tide in cerebellar memory formation. Curr Opin Neurobiol 15:667–74.

Dobkin BH, Havton LA. 2004. Basic advances and new avenues in therapy of spinal cord injury. Ann Rev Med 55:255–82.

Dunlop SA. 2008. Activity-dependent plasticity: implications for recovery after spinal cord injury. Trends Neurosci 31:410–8.

Evatt ML, Wolf SL, Segal RL. 1989. Modification of human spinal stretch reflexes: preliminary studies. Neurosci Lett 105:350–5.

Falvell SW, Greenberg ME. 2008. Signaling mechanisms linking neuronal activity to gene expression and plasticity of the nervous system. Ann Rev Neurosci 31:563–90.

Fouad K, Tse A. 2008. Adaptive changes in the injured spinal cord and their role in promoting functional recovery. Neurol Res 30:17–27.

Froemke RC, Merzenich MM, Schreiner CE. 2007. A synaptic memory trace for cortical receptive field plasticity. Nature 450:425–9.

Ge S, Sailor KA, Ming GL, Song H. 2008. Synaptic integration and plasticity of new neurons in the adult hippocampus. J Physiol 586:3759–65.

Graybiel AM. 2005. The basal ganglia: learning new tricks and loving it. Curr Opin Neurobiol 15:638–44.

Green JT, Woodruff-Pak DS. 2000. Eyeblink classical conditioning: hippocampal formation is for neutral stimulus associations as cerebellum is for association-response. Psych Bull 126:138–58.

Guo W, Wang H, Watanabe M, Shimizu K, Zou S, LaGraize SC, and others. 2007. Glial-cytokine-neuronal interactions underlying the mechanisms of persistent pain. J Neurosci 27:6006–18.

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

Henneman E, Mendell LM. 1981. Functional organization of motoneuron pool and inputs. In: Brooks VB, editor. Handbook of physiology. Section I: the nervous system. Volume II: motor control, part I. Baltimore: Williams and Wilkins. p 423–507.

Holtmaat A, Svoboda K. 2009. Experience-dependent structural synaptic plasticity in the mammalian brain. Nat Rev Neurosci 10:647–58.

Illing RB. 2001. Activity-dependent plasticity in the adult auditory brainstem. Audiol Neurootol 6:319–45.

Isaacs KR, Anderson BJ, Alcantara AA, Black JE, Greenough WT. 1992. Exercise and the brain: angiogenesis in the adult rat cerebellum after vigorous physical activity and motor skill learning. J Cereb Blood Flow Metab 12:110–9.

Jenkins JJ. 1985. Nonsense syllables: comprehending the "almost incomprehensible variation." J Exp Psychol Learn Mem Cogn 11:455–60.

Johnson MV. 2009. Plasticity in the developing brain: implications for rehabilitation. Dev Dis Res Rev 15:94–101.

Jones EG. 2000. Cortical and subcortical contributions to activity-dependent plasticity in primate somatosensory cortex. Ann Rev Neurosci 23:1–37.

Kaas JH, Qi HX, Burish MJ, Gharbawie OA, Onifer SM, Massey JM. 2008. Cortical and subcortical plasticity in the brains of humans, primates, and rats after damage to sensory afferents in the dorsal columns of the spinal cord. Exp Neurol 209:407–16.

Knikou M. 2008. The H-reflex as a probe: pathways and pitfalls. J Neurosci Meth 171:1–12.

Knott G, Holtmaat A. 2008. Dendritic spine plasticity: current understanding from in vivo studies. Brain Res Rev 58: 282–9.

Koceja DM, Markus CA, Trimble MH. 1995. Postural modulation of the soleus H reflex in young and old subjects. Electroencephalogr Clin Neurophysiol 97:387–93.

Koh HY, Weiss KR. 2007. Activity-dependent peptidergic modulation of the plateau-generating neuron B64 in the feeding network of Aplysia. J Neurophysiol 97:1862–7.

Kreitzer AC, Makenka RC. 2008. Striatal plasticity and basal ganglia circuit function. Neuron 60:542–54.

Kuczewski N, Porcher C, Ferrand N, Florentino H, Pelligrino C, Kolarow R, and others. 2008. Backpropagating action potentials trigger dendritic release of BDNF during spontaneous network activity. J Neurosci 28:7013–23.

Kuczewski N, Porcher C, Lessmann V, Medina I, Gaiarsa JL. 2009. Activity-dependent dendritic release of BDNF and biological consequences. Molec Neurobiol 39:37–49.

Lange-Asschenfeldt C, Kojda G. 2008. Alzheimer's disease, cerebrovascular dysfunction and the benefits of exercise: from vessels to neurons. Exp Gerontol 43:499–504.

Lapash Daniels CM, Ayers KL, Finley AM, Culver JP, Goldberg MP. 2009. Axon sprouting in adult mouse spinal cord after motor cortex stroke. Neurosci Lett 450:191–5.

Leonard JL, Edstrom JP. 2004. Parallel processing in an identified neural circuit: the Aplysia californica gill-withdrawal response model system. Biol Rev Camb Philos Soc 79:1–59.

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

Lindholm D, Castrén E, Berzaghi M, Blöchl A, Thoenen H. 1994. Activity-dependent and hormonal regulation of neurotrophin mRNA levels in the brain: implications for neuronal plasticity. J Neurobiol 25:1362–72.

Lledo PM, Saghatelyan A. 2005. Integrating new neurons into the adult olfactory bulb: joining the network, life-death decisions, and the effects of sensory experience. Trends Neurosci 28:248–54.

Lushnikova I, Skibo G, Muller G, Nikonenko I. 2009. Synaptic potentiation induces increased glial coverage of excitatory synapse in CA1 hippocampus. Hippocampus 19:753–62.

Lynskey JV, Belanger A, Jung R. 2008. Activity-dependent plasticity in spinal cord injury. J Rehabil Res Dev 45:229–40.

Ma DK, Kim WE, Ming GL, Song H. 2009. Activity-dependent extrinsic regulation of adult olfactory bulb and hippocampal neurogenesis. Ann NY Acad Sci 1170:664–73.

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.

Marder E, Abbott LF, Turrigiano GG, Liu Z, Goldwasch J. 1996. Memory from the dynamics of intrinsic membrane currents. Proc Natl Acad Sci 93:13481–6.

Martin JH, Friel KM, Salimi I, Chakrabarty S. 2007. Activity- and use-dependent plasticity of the developing corticospinal system. Neurosci Biobehav Rev 31:1125–35.

Matsuura K, Zhang B, Mori T, Smith EL 3rd, Kaas JH, Chino Y. 2002. Topographic map reorganization in cat area 17 after early monocular retinal lesions. Vis Neurosc 19:85–96.

Matthews PBC. 1972. Mammalian muscle receptors and their central actions. Baltimore: Williams & Wilkins. p 319–409.

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

Meunier S, Kwon J, Russmann H, Ravindran S, Mazzocchio R, Cohen L. 2007. Spinal use-dependent plasticity of synaptic transmission in humans after a single cycling session. J Physiol 579(Pt 2):375–88.

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.

Myklebust BM, Gottlieb GL, Agarwal GC. 1986. Stretch reflexes of the normal human infant. Dev Med Child Neurol 28:440–9.

Nelson CA. 2001. The development and neural bases of face recognition. Infant Child Dev 10:3–18.

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.

O'Sullivan MC, Miller S, Ramesh V, Conway E, Gilfillan K, McDonough S, and others. 1998. Abnormal development of biceps brachii phasic stretch reflex and persistence of short latency heteronymous reflexes from biceps to triceps brachii in spastic cerebral palsy. Brain 121:2381–95.

Palmer TD, Willhoite AR, Gage FH. 2000. Vascular niche for adult hippocampal neurogenesis. J Comp Neurol 425: 479–94.

Parker D. 2000. Spinal-cord plasticity: independent and interactive effects of neuromodulator and activity-driven plasticity. Molec Neurobiol 22:55–80.

Pomerantz FR, Wolpaw JR, Lichtman SW, DeFrancesco E, Thompson A. 2009. Operant conditioning of the soleus H-reflex in spastic subjects after incomplete spinal cord injury. Program no. 79.9. Washington, DC: Society for Neuroscience Online.

Raineteau O. 2008. Plastic responses to spinal cord injury. Behav Brain Res 192:114–23.

Rossignol S, Bouyer L, Barthelemy D, Langlet C, Leblond H. 2002. Recovery of locomotion in the cat following spinal cord lesions. Brain Res Rev 40:257–66.

Rygh LJ, Suzuki R, Rahman W, Wong Y, Vonsy JL, Sandhu H, and others. 2006. Local and descending circuits regulate long-term potentiation and zif268 expression in spinal neurons. Eur J Neurosci 24:761–72.

Rygh LJ, Svendsen F, Fiska A, Haugan F, Hole K, Tjolsen A. 2005. Long-term potentiation in spinal nociceptive systems: how acute pain may become chronic. Psychoneuroendocrinology 30:959–64.

Sadowski CL, McDonald JW. 2009. Activity-based restorative therapies: concepts and applications in spinal cord injury-related neurorehabilitation. Dev Dis Res Rev 15:112–6.

Schneider S, Capaday C. 2003. Progressive adaptation of the soleus H-reflex with daily training at walking backward. J Neurophysiol 89:648–56.

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

Stein RB, Misiaszek JE, Pearson KG. 2000. Functional role of muscle reflexes for force generation in the decerebrate walking cat. J Physiol 525:781–91.

Steinmetz JE. 2000. Brain substrates of classical eyeblink conditioning: a highly localized but also distributed system. Behav Brain Res 110:13–24.

Tan J, Widjaja S, Xu J, Shepherd RK. 2008. Cochlear implants stimulate activity-dependent CREB pathway in the deaf auditory cortex: implications for molecular plasticity induced by neural prosthetic devices. Cereb Cortex 18:1799–813.

Tashiro A, Makino H, Gage FH. 2007. Experience-specific functional modification of the dentate gyrus through adult neurogenesis: a critical period during an immature stage. J Neurosci 27:5845–6.

Theodosis DT, Poulain DA, Oloet SH. 2008. Activity-dependent structural and functional plasticity of astrocyte-neuron interactions. Physiol Rev 88:983–1008.

Thompson AK, Chen XY, Wolpaw JR. 2009. Acquisition of a simple skill: task-dependent adaptation plus long-term change in the human soleus H-reflex. J Neurosci 29:5784–92.

Tropea D, Kreiman G, Lyckman A, Mukherjee S, Yu H, Horng S, and others. 2006. Gene expression changes and molecular pathways mediating activity-dependent plasticity in the visual cortex. Nat Neurosci 9:660–8.

Wang Y, Pillai S, Wolpaw JR, Chen XY. 2006. Motor learning changes GABAergic terminals on spinal motoneurons in normal rats. Eur J Neurosci 23:141–50.

Wang Y, Pillai S, Wolpaw JR, Chen XY. 2009. H-reflex down-conditioning greatly increases the number of identifiable GABAergic interneurons in rat ventral horn. Neurosci Lett 452:124–9.

Waxman SG. 2000. The neuron as a dynamic electrogenic machine: modulation of sodium-channel expression as a basis for functional plasticity in neurons. Phil Trans Royal Soc Lond B Biol Sci 355:199–213.

Whitaker VR, Cui L, Miller S, Yu SP, Wei L. 2007. Whisker stimulation enhances angiogenesis in the barrel cortex following focal ischemia in mice. J Cereb Blood Flow Metab 27:57–68.

Wickens JR. 2009. Synaptic plasticity in the basal ganglia. Behav Brain Res 199:119–28.

Willis WD. 2002. Long-term potentiation in spinothalamic neurons. Brain Res Brain Res Rev 40:202–14.

Wolpaw JR. 1987. Operant conditioning of primate spinal reflexes: the H reflex. J Neurophysiol 57:443–58.

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

Wolpaw JR. 2002. Memory in neuroscience: rhetoric versus reality. Behav Cog Neurosci Rev 1:130–63.

Wolpaw JR. 2006. Education and reeducation of the spinal cord. Prog Brain Res 157:261–80.

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

Wolpaw JR, Chen XY. 2001. Operant conditioning of rat H-reflex: effects on mean latency and duration. Exp Brain Res 136:274–9.

Wolpaw JR, Chen XY. 2006. The cerebellum in maintenance of a motor skill: a hierarchy of brain and spinal cord plasticity underlies H-reflex conditioning. Learn Mem 13:208–15.

Wolpaw JR, Chen XY. 2009. Operant conditioning of reflexes. Academic Press encyclopedia of neuroscience. Vol. 7. Oxford: Academic Press. p 225–33.

Wolpaw JR, Herchenroder PA. 1990. Operant conditioning of H-reflex in freely moving monkeys. J Neurosci Meth 31: 145–52.

Wolpaw JR, Herchenroder PA, Carp JS. 1993. Operant conditioning of the primate H-reflex: factors affecting the magnitude of change. Exp Brain Res 97:31–9.

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.

Wolpaw JR, Tennissen AM. 2001. Activity-dependent spinal cord plasticity in health and disease. Ann Rev Neurosci 24: 807–43.

Xu J, Kang J. 2005. The mechanisms and functions of activity-dependent long-term potentiation of intrinsic excitability. Rev Neurosci 16:311–23.

Yang JF, Stein RB, James KB. 1991. Contribution of peripheral afferents to the activation of the soleus H-reflex in walking in humans. Exp Brain Res 87:679–87.

Zhang XC, Zhang YQ, Zhao ZQ. 2006. Different roles of two nitric oxide activated pathways in spinal long-term potentiation of C-fiber-evoked field potentials. Neuropharmacology 50:748–54.

Zhang W, Linden DJ. 2003. The other side of the engram: experience-driven changes in neuronal intrinsic excitability. Nat Rev Neurosci 4:885–900.

Zehr EP. 2002. Considerations for use of the Hoffman reflex in exercise studies. Eur J Appl Physiol 86:455–68.