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The Simplest Motor Skill: Mechanisms and Applications of Reflex Operant Conditioning

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Abstract

Operant conditioning protocols can gradually change spinal reflexes, which are the simplest behaviors. This article summarizes the evidence supporting two propositions: that these protocols provide excellent models for defining the substrates of learning; and that they can induce and guide plasticity to help restore skills such as locomotion that have been impaired by spinal cord injury or other disorders.

Keywords

Skill acquisition; H-reflex; spinal cord plasticity; learning; locomotion; spinal cord injury

Introduction

Over the past several decades, the ubiquity of activity-dependent plasticity in the central nervous system (CNS) has become increasingly evident. The traditional view of the CNS as a hard-wired structure that changes only in limited ways and at a few locations has been overturned; it is now clear that plasticity occurs throughout the CNS and throughout life (reviewed in (31,33)). Along with this change has come recognition that the plasticity associated with motor skill acquisition is not limited to the cerebral cortex, or even to the entire brain, but rather extends all the way down to the spinal cord (reviewed in (31,33,34)). In fact, athletic training or motor skill acquisition induces plasticity in spinal cord pathways (e.g., spinal reflexes). For example, long- and short-distance runners have significantly smaller gastrocnemius H- and T-reflexes than non-trained subjects (13) and ballet dancers have smaller soleus H-reflexes than other highly trained athletes (12). Such training-induced plasticity in spinal reflexes also occurs after spinal cord injury or with other CNS disorders ((7,26) see also (5,18)).

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In sum, extensive training or skill acquisition that repeats certain patterns of peripheral sensory and/or descending inputs to the spinal cord induces plasticity that shapes the activity of spinal reflex pathways, and may also affect activity elsewhere in the CNS (reviewed in (31,34)). Thus, to understand the mechanisms of motor skill acquisition, it is important to understand how plasticity is induced and guided at many different sites, including spinal cord pathways, and how these many changes combine to produce the new skill while at the same time maintaining existing skills. In this article, we review evidence indicating that operant conditioning of spinal reflexes is an excellent model for elucidating the mechanisms of skill acquisition and that it can also enhance neurorehabilitation by inducing and guiding beneficial plasticity.

Advantages Of Using A Spinal Reflex To Study Motor Skill Learning And Memory

Spinal reflexes, the simple behaviors mediated entirely by spinal cord pathways, have unique advantages for studying mechanisms of motor skill acquisition. First, activity-dependent plasticity is abundant in the spinal cord (10,14,17,18,32,33). It is induced and guided by inputs to the spinal cord from the brain and the periphery; these inputs gradually establish and maintain spinal cord circuits in a state that supports the entire roster of motor behaviors (33). This gradual activity-dependent plasticity shapes spinal cord function during development, throughout later life, in response to trauma and disease, and during motor function recovery after CNS or peripheral damage (5,15-18,33,34). Second, the relative simplicity and accessibility of the spinal cord and its distance from the brain facilitate study of individual components of this multisite plasticity. The major neuronal populations and pathways of the spinal cord are well known and accessible to monitoring. Furthermore, the anatomical separation of brain and spinal cord makes it possible to study interactions between supraspinal and spinal plasticity that underlie skill acquisition and maintenance. Finally and most importantly, spinal cord pathways participate in essentially all behaviors. The spinal cord is the place where multiple supraspinal and peripheral inputs are integrated into the activations of motoneurons (and the resulting muscle contractions) that comprise motor behaviors.

Acquisition Of The Simplest Motor Skill:Operant Conditioning Of A Spinal Reflex

While spinal reflexes normally function as components of complex skills such as locomotion, they are themselves simple behaviours produced by pathways entirely within the spinal cord (20,35). These pathways are influenced in both the short-term and the long-term by descending inputs from the brain. In the short-term, they undergo task-dependent modulation as the animal or human switches from one behavior to another (20,21)). In the long-term, the brain shapes spinal reflex pathways so that they serve new skills and maintain old ones (31,33). Thus, at any given moment, spinal reflex function reflects both short-term task-dependent adaptations and long-term plasticity.

Operant conditioning, in which modification of a behavior is brought about by the consequence of that behavior, is a powerful method to induce learning. Through operant conditioning, even the simplest behaviors, such as spinal reflex behaviors, can be changed. Operant conditioning of a spinal reflex can provide an excellent experimental model for studying learning and memory: its key elements consist of a spinal cord reflex; supraspinal influence over that pathway; and the spinal cord plasticity induced by that influence (32). By basing reward on reflex size, the conditioning protocol operantly conditions the brain to provide supraspinal influence that appropriately affects reflex size.

Over the past 30 years, operant conditioning of the simplest spinal cord reflex, the spinal stretch reflex (SSR) (i.e., the “knee-jerk” reflex), or its electrical analog, the Hoffmann (or H-) reflex has been studied in monkeys, rats, mice, and humans (24,30,32). Figure 1A illustrates this pathway. If the group I (largely 1A) afferents are excited by muscle stretch, the response is the SSR; if they are excited by electrical stimulation of the nerve, the response is the H-reflex (6,8). It should be noted that the SSR and H-reflex do or might differ somewhat in other respects as well: only the SSR is affected by γ-motoneuron mediated fusimotor control; and the two reflexes are likely to differ in their distributions of active group I afferents (i.e., Ia vs. Ib) and/or in the synchrony of afferent excitations (e.g., (9,11)). Nevertheless, both the SSR and H-reflex can be increased or decreased by an operant conditioning protocol (30-32). Regardless of the species (i.e., human, monkey, rat, or mouse), the standard protocol operantly conditions the subject to increase (or decrease) reflex size by rewarding the subject for a larger (or smaller) reflex. The reward contingency ensures that supraspinal influence that increases (or decreases) the reflex is rewarded while influence that decreases (or increases) it is not. As a result, supraspinal influence that increases (or decreases) the reflex becomes more prevalent, and gradually changes the spinal cord. For reasons of experimental and clinical practicality, most work has focused and continues to focus on conditioning the H-reflex rather than the SSR.

The rat soleus H-reflex conditioning protocol is briefly summarized here (the monkey and mouse protocols are similar). The rat is chronically implanted with fine-wire EMG electrodes in the soleus muscle and a stimulating cuff on the posterior tibial nerve. The implanted wires connect through a head-mount and a flexible tether and commutator to EMG amplifiers and a nerve-cuff simulator. Soleus EMG activity is monitored continuously (24/7) in the freely moving animal. Whenever the absolute soleus EMG activity remains within a specified range for a randomly varying 2.3-2.7 s period, a nerve-cuff stimulus elicits the M-wave and the H-reflex. The stimulus level is kept just above M-wave threshold. Typically, the animal provides 2500-8000 H-reflex trials per day.

For the first 10 days, the rat is exposed to the control mode, in which no reward occurs and the H-reflex is simply measured to determine its baseline value. For the next 50 days, the rat is exposed to the up-conditioning (HRup) or down-conditioning (HRdown) mode, in which a food reward occurs if the H-reflex is above (HRup) or below (HRdown) a criterion value. Background EMG level and M-wave amplitude remain constant throughout. Because the H-reflex is the earliest possible CNS response to the nerve stimulus, the animal can modify H-reflex size only by being prepared ahead of time, that is, by maintaining mode-appropriate supraspinal influence over the reflex pathway. This influence (most likely exerted by

descending corticospinal tract (CST) activity, see the section below) gradually induces activity-dependent plasticity in the spinal cord, resulting in gradual operantly conditioned H-reflex change.

Figure 1C shows the results of operant conditioning in different species. In each species, exposure to the up-(▲) or down-(▼) conditioning paradigm gradually changes the size of the reflex in the correct direction. Successful conditioning (i.e., >20% change in the correct direction (30)) occurs in 75-80% of the animals. In the remaining animals, the reflex size remains within 20% of its baseline value. The central finding is that operant conditioning changes the size of the reflex appropriately for the conditioning mode (either up or down) over days and weeks. According to a standard definition of a skill as an adaptive behavior acquired through practice (Compact Oxford English Dictionary 1993), the larger (up-conditioned) or smaller (down-conditioned) reflex created by this operant conditioning protocol is a simple motor skill.

Operant Conditioning Of The Soleus H-Reflex In Humans

In humans, reflex operant conditioning was applied first to the biceps brachii stretch reflex (19) and more recently to the soleus H-reflex (24). The human H-reflex conditioning protocol in humans is comparable to that in animals, except for the number of trials; humans perform only 675 trials/wk (i.e., only 2-5% as many as animals) and these trials are confined to three 1-hr sessions. The standard protocol comprises six baseline sessions and 24 conditioning sessions at a rate of 3 sessions per week, and four follow-up sessions over the next three months.

In each session, the soleus H-reflex is elicited while the standing subject maintains soleus background EMG at a defined stable level (i.e., natural standing level) (Figure 2). M-wave size is kept constant for all the H-reflex trials within and between sessions. In each baseline session, three blocks of 75 control H-reflex trials (i.e., 225 H-reflexes) occur. In each conditioning or follow-up session, 20 within-session control H-reflexes are measured as in the baseline sessions and then three blocks of 75 (i.e., 225) conditioned H-reflex trials occur. In these conditioned H-reflex trials, the subject is encouraged to increase (HRup mode) or decrease (HRdown mode) H-reflex size and is given visual feedback after each stimulus (Figure 2) that indicates whether the H-reflex was larger (HRup mode) or smaller (HRdown mode) than a criterion value. A high frequency of success in satisfying the criterion earns an additional monetary reward. Background EMG and M-wave size are kept stable throughout data collection.

In contrast to the standard animal protocol, this human protocol allows us to distinguish between and track the development of two different components of H-reflex change. The conditioned H-reflexes track the overall development of H-reflex conditioning, the control H-reflexes tracks the development of gradual across-session change, and the within-session differences between the conditioned and control H-reflexes track the development of rapid task-dependent adaptation.

Figure 3 summarizes the results of soleus H-reflex conditioning in neurologically normal subjects. Over the 24 conditioning sessions, H-reflex size gradually increased in 6 of 8

HRup subjects and decreased in 8 of 9 HRdown subjects, resulting in final sizes of 140(±12SEM)% and 69(±6)% of baseline size, respectively. In these subjects, the final H-reflex change was the sum of within-session change (i.e., task-dependent adaptation) and across-session (i.e., long-term) change. Task-dependent adaptation appeared within 4-6 sessions and persisted unchanged thereafter, averaging +13% in HRup subjects and -15% in HRdown subjects. In contrast, long-term change began after 10-12 sessions and increased gradually thereafter, reaching +27% in HRup subjects and -16% in HRdown subjects. (See (24) for complete presentation and discussion of task-dependent adaptation and long-term change.)

This study showed that human subjects performing only 225 reflex conditioning trials per day, 3 days a week, displayed gradual reflex change similar in course and nearly equal in magnitude to that of animals that performed 20-50 times as many trials. This finding shows that H-reflex conditioning is possible in humans, and that it does not require the several thousand trials per day typically completed by animals. (Animals probably do not need that many trials either, but that remains to be determined.) The success rate of 82% (i.e., 14 of 17 subjects changed H-reflex size significantly in the correct direction, while H-reflex size did not change significantly in the other 3 subjects) was also similar to that of animals (24,30).

In addition to its demonstration of H-reflex conditioning in humans, the major significance of this study is that it dissects the course of a simple skill acquisition (i.e., a larger or smaller H-reflex) and thereby distinguishes two phenomena, rapid task-dependent adaptation and gradual long-term change, that constitute the skill. Task-dependent adaptation and long-term change differ in time of onset and rate of development. Task-dependent adaptation can be turned on or off rapidly while long-term change occurs gradually and persists for months after conditioning ends. Together with previous animal studies, these findings suggest that task-dependent adaptation reflects supraspinal plasticity (that may change the H-reflex by modifying presynaptic inhibition at the Ia-motoneuron synapse) (24,32) and that long-term change reflects plasticity in the spinal cord (e.g., in motoneuron properties) ((27,32) for discussion).

It is worth emphasizing that recognizing the development of each of these two components separately was possible because each conditioning session of the human protocol measured the H-reflex without and with task-dependent adaptation (i.e., the within-session control trials and the conditioning trials, respectively), unlike the animal protocol, which simply imposed the conditioning task for the entire conditioning period. (Although the overall course of reflex change in animals strongly suggested the presence of these two components (32).)

Another recent study examined the impact of H-reflex conditioning on the entire H-reflex recruitment curve (25). Operant conditioning of the human soleus H-reflex changed all or most of the H-reflex recruitment curve. Depending on the individual, the change was an overall positive (with HRup) or negative (with HRdown) shift in the curve (e.g., Figure 3D) or a leftward (with HRup) or rightward (with HRdown) shift (not shown). Since these H-reflex recruitment curves were measured before the conditioning trials, while the subject simply maintained the background EMG level and did not try to change the H-reflex, the H-

reflexes changes found in this control situation reflect long-term plasticity produced by the conditioning sessions (24). These results are also consistent with previous data showing that H-reflex conditioning affects the pathway's participation in other motor behaviors, such as locomotion (32).

The Complex Plasticity Associated With Spinal Reflex Conditioning

An ongoing series of animal studies is revealing the complex patterns of spinal and supraspinal plasticity underlying H-reflex conditioning (30-33). A positive shift in motoneuron firing threshold (possibly resulting from a change in the activation voltage of Na^+ channels) can largely account for H-reflex down-conditioning (reviewed in (30)). Down-conditioning is also accompanied by marked increases in identifiable GABAergic interneurons in the ventral horn and GABAergic terminals on the soleus motoneuron (32). Additional changes occur in several other synaptic populations on the motoneuron, in motor unit properties, in other spinal interneurons, and even on the contralateral side of the spinal cord (30). Interestingly, up-conditioning and down-conditioning are not mirror images of each other; they appear to have different mechanisms. Up-conditioning may result from plasticity in spinal interneurons (32).

The corticospinal tract (CST) is the only major descending tract essential for H-reflex conditioning (32). Given its rapid development and ability to be turned on and off quickly, task-dependent adaptation (or phase-1 change (32)) in the H-reflex is likely to reflect acute change in CST activity. This (or related) CST activity is likely to be responsible for gradually inducing the spinal cord plasticity underlying long-term (or phase-2)(24,32)) change in the H-reflex. Furthermore, it is clear that plasticity occurs also in sensorimotor cortex or related brain areas, and that both the cerebellum and the basal ganglia play important roles (32). In sum, the simple skill of a larger or smaller H-reflex rests on a hierarchy of brain and spinal cord plasticity (32). The operant conditioning protocol induces and maintains the plasticity in the brain that produces the CST activity that induces and maintains the spinal cord plasticity that is directly responsible for most of the change in H-reflex size (24,32). Figure 4 summarizes current understanding of the hierarchy of plasticity that underlies H-reflex conditioning.

The Impact Of A New Skill On Older Skills

When H-reflex conditioning changes the spinal reflex pathway, it is likely to affect previously acquired behaviors, such as locomotion, that also use this pathway. Indeed, soleus H-reflex conditioning in normal rats changes locomotor EMG activity and kinematics (e.g., ankle angle) (1). Nevertheless, key features of locomotion, such as right/left symmetry in the timing of the step-cycle and in hip heights, are preserved (32). These features appear to be preserved by *compensatory* plasticity that prevents the *primary* plasticity (i.e., the plasticity directly responsible for soleus H-reflex change) from disrupting locomotion (32). For example, the change in ankle angle associated with the altered soleus H-reflex pathway is accompanied by reciprocal change in hip angle, which prevents change in hip height (1); and a conditioning-induced change in the soleus H-reflex is usually accompanied by an opposite change in the quadriceps H-reflex (1).

These findings support the hypothesis that the functional properties of spinal pathways are maintained in a state of "*negotiated equilibrium*," a balance that ensures the satisfactory performance of all the behaviors in the individual's current repertoire (32). Acquisition of a new behavior (or skill) (e.g., a larger or smaller H-reflex) requires the creation of a new equilibrium that accommodates the H-reflex change and also continues to serve previously acquired skills. Prior to a new skill acquisition, spinal pathways are in the state of equilibrium that is a product of previous skill acquisitions and serves each of them satisfactorily. When acquisition of a new skill changes spinal pathways and thereby disturbs older skills, it induces compensatory plasticity that preserves the key features of the older skills. The plasticity that preserves each older skill may in turn affect other skills and lead to further plasticity. The culmination of this iterative process, or negotiation, is a new spinal cord equilibrium that satisfies each skill in the expanded repertoire.

Therapeutic Applications Of Spinal Reflex Conditioning

Operant conditioning of a spinal reflex can modify the activity of spinal cord pathways and can thereby affect behaviors that use these pathways. Furthermore, it is now clear that learning the simple skill of a larger or smaller H-reflex creates a hierarchy of complex multi-site plasticity from the brain to the spinal cord (31,32). This multi-site plasticity involves pathways that play important roles in other behaviors, such as locomotion. Thus, an appropriately designed reflex conditioning protocol might ameliorate movement disabilities due to CNS damage. Indeed, in rats with abnormal locomotion due to incomplete spinal cord injury (SCI), appropriate soleus H-reflex conditioning can restore more normal locomotion (32).

In an early study, Segal and Wolf (19) showed that the biceps brachii spinal stretch reflex could be operantly conditioned in people with incomplete SCI. To determine whether reflex conditioning could improve motor function in those with incomplete SCI, we recently studied the feasibility and the functional impact of down-conditioning the soleus H-reflex in people with impaired locomotion caused by chronic incomplete SCI (27).

In people with chronic incomplete SCI, spasticity is often expressed as exaggerated stretch reflexes and abnormal reflex modulation in the ankle extensor muscles (3,22). Normally, spinal reflexes are modulated from standing to walking, and during walking reflexes are further modulated across the different phases of the step cycle (21,35). However, in people with SCI, modulation of the soleus H-reflex across the step-cycle is often absent or greatly diminished (i.e., H-reflex amplitude remains high even in the early stance or swing phase, where the H-reflex is normally very small or absent) (22) and this abnormality appears to affect locomotor EMG activity, contributing to clonus, foot-drop, and other disabling problems (3,22). These findings suggest that decreasing reflex excitability in the spastic extensor muscles by operant down-conditioning might alleviate spastic gait in this population.

Our subjects were ambulatory adults with chronic incomplete SCI whose gaits were impaired by ankle extensor spasticity and hyperreflexia. The H-reflex conditioning protocol was the same as the one used in normal subjects (24), except that the number of conditioning

sessions was increased from 24 to 30. The six baseline and 30 conditioning sessions occurred at the rate of 3 sessions per week for 12 weeks. Soleus and tibialis anterior background EMG and soleus M- wave size were kept constant throughout the study. After the baseline period in which soleus H-reflex size was measured and locomotion was assessed, the subjects completed either 30 H-reflex down-conditioning sessions (DC subjects) or 30 control sessions in which the H-reflex was simply measured (Unconditioned (UC) subjects), and locomotion was reassessed.

Over the 30 sessions, the soleus H-reflex decreased in 6 of 9 DC subjects (Figure 5 and 6) and remained smaller several months later. In these subjects, locomotion became significantly faster and more symmetrical (Figure 7), and locomotor EMG modulation increased bilaterally. Furthermore, beginning about halfway through the conditioning sessions, all of these subjects commented spontaneously that they were walking faster and farther in their daily lives, and several noted less clonus, easier stepping, less arm weight-bearing, and/or other improvements. The H-reflex did not decrease in the other DC subjects or in any of the UC subjects (Figure 5A), and their locomotion did not improve. These results indicated that the beneficial impact of H-reflex conditioning extended well beyond the effects that could be ascribed to change in the soleus H-reflex pathway (e.g., locomotor EMG modulation increased in contralateral muscles). In terms of the negotiated equilibrium hypothesis summarized above (32), it appears that the iterative process (i.e. the new negotiation) triggered by the acquisition of the new skill (i.e., a smaller soleus H-reflex), led to a new equilibrium superior to that prior to H-reflex conditioning (see (32) for discussion). In sum, this initial study suggests that reflex conditioning protocols can enhance motor function recovery after incomplete SCI and possibly in other disorders as well.

There are several compelling reasons to pursuit the development of reflex conditioning as a new rehabilitation approach. Because reflexes can be increased or decreased and different reflex pathways can be targeted by these protocols (i.e., not simply the H-reflex pathway), a protocol might be customized for each individual to address his/her motor control problems. For example, in rats with SCI in which locomotion was impaired by weak stance, up-conditioning of the soleus H-reflex strengthened stance and restored gait symmetry (32); in contrast, in people with SCI in whom locomotion was impaired by ankle extensor spasticity, down-conditioning of the soleus H-reflex restored gait symmetry and increased walking speed (27). It should also be possible to design reflex conditioning protocols that complement existing therapeutic training methods, such as treadmill training (4,28) and constraint-induced movement therapy (23,29), in order to maximize the recovery of useful motor function. Reflex conditioning protocols might also enhance recovery after other kinds of trauma, such as peripheral nerve transection (2).

Furthermore, when CNS regeneration therapy becomes possible, methods such as spinal reflex conditioning could be essential for re-educating newly regenerated connections to function effectively. Without appropriate induction and guidance of activity-dependent plasticity, regenerated connections are likely to display diffuse infantile-like responses and dysfunctional motor outputs (reviewed in (31-33)). As mentioned above, operant conditioning produces complex patterns of multi-site plasticity that extend well beyond the

targeted reflex pathway (32). Thus, it is essential to delineate the principles critical for designing reflex conditioning protocols appropriate for individual patients.

Summary

Operant conditioning is a powerful method for inducing motor skill learning. Through operant conditioning, even the simplest motor behaviors, such as spinal reflex behaviors, can be changed. Because the spinal cord is relatively simple and technically accessible and is connected to the brain by well-defined pathways, operant conditioning of a spinal reflex provides an excellent experimental model for studying learning and memory: it is possible to identify the critical spinal cord plasticity; to determine its dependence on influence from the brain; and to begin to delineate the hierarchy of brain and spinal cord plasticity underlying the learning. Spinal reflex conditioning affects other behaviors such as locomotion that use the same pathway. Thus, in normal subjects, it induces additional plasticity that preserves the key features of these behaviors. Furthermore, in subjects in whom trauma or disease (e.g., an incomplete spinal cord injury) has impaired the key features of a behavior, appropriate reflex conditioning can induce and guide plasticity that improves these features. Reflex conditioning protocols may provide an important new therapeutic approach that can complement other rehabilitation methods and augment recovery of useful function.

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References

1. Chen Y, Chen L, Wang Y, Wolpaw JR, Chen XY. Operant conditioning of rat soleus H-reflex oppositely affects another H-reflex and changes locomotor kinematics. J Neurosci. 2011; 31:11370–11375. [PubMed: 21813696]
2. Chen Y, Wang Y, Chen L, Sun C, English AW, Wolpaw JR, Chen XY. H-reflex upconditioning encourages recovery of EMG activity and H-reflexes after sciatic nerve transection and repair in rats. J Neurosci. 2010; 30:16128–16136. [PubMed: 21123559]
3. Dietz V, Sinkjaer T. Spastic movement disorder: impaired reflex function and altered muscle mechanics. Lancet Neurol. 2007; 6:725–733. [PubMed: 17638613]
4. Edgerton VR, Courtine G, Gerasimenko YP, Lavrov I, Ichiyama RM, Fong AJ, Cai LL, Otoshi CK, Tillakaratne NJ, Burdick JW, et al. Training locomotor networks. Brain Res Rev. 2008; 57:241–254. [PubMed: 18022244]
5. Frigon A, Barriere G, Leblond H, Rossignol S. Asymmetric changes in cutaneous reflexes after a partial spinal lesion and retention following spinalization during locomotion in the cat. J Neurophysiol. 2009; 102:2667–2680. [PubMed: 19726726]
6. Henneman, E.; Mendell, LM. Handbook of Physiology: Section 1: The Nervous System Volume II, Part 1 &2: Motor Control. American Physiological Society; 1980. Functional organization of motoneuron pool and its inputs.; p. 423-507.
7. Hodapp M, Vry J, Mall V, Faist M. Changes in soleus H-reflex modulation after treadmill training in children with cerebral palsy. Brain. 2009; 132:37–44. [PubMed: 18984603]
8. Magladery JW, Porter WE, Park AM, Teasdall RD. Electrophysiological studies of nerve and reflex activity in normal man. IV. The two-neurone reflex and identification of certain action potentials from spinal roots and cord. Bull Johns Hopkins Hosp. 1951; 88:499–519. [PubMed: 14839348]

9. McKeon B, Burke D. Muscle spindle discharge in response to contraction of single motor units. J Neurophysiol. 1983; 49:291–302. [PubMed: 6220135]
10. Mendell LM. Modifiability of spinal synapses. Physiol Rev. 1984; 64:260–324. [PubMed: 6320234]
11. Morita H, Petersen N, Christensen LO, Sinkjaer T, Nielsen J. Sensitivity of H-reflexes and stretch reflexes to presynaptic inhibition in humans. J Neurophysiol. 1998; 80:610–620. [PubMed: 9705454]
12. Nielsen J, Crone C, Hultborn H. H-reflexes are smaller in dancers from The Royal Danish Ballet than in well-trained athletes. Eur J Appl Physiol Occup Physiol. 1993; 66:116–121. [PubMed: 8472692]
13. Ozmerdivenli R, Bulut S, Urat T, Ayar A. The H- and T-reflex response parameters of long- and short-distance athletes. Physiol Res. 2002; 51:395–400. [PubMed: 12449438]
14. Pearson KG. Plasticity of neuronal networks in the spinal cord: modifications in response to altered sensory input. Prog Brain Res. 2000; 128:61–70. [PubMed: 11105669]
15. Raineteau O. Plastic responses to spinal cord injury. Behav Brain Res. 2008; 192:114–123. [PubMed: 18372052]
16. Raineteau O, Schwab ME. Plasticity of motor systems after incomplete spinal cord injury. Nat Rev Neurosci. 2001; 2:263–273. [PubMed: 11283749]
17. Rossignol S, Frigon A. Recovery of locomotion after spinal cord injury: some facts and mechanisms. Annu Rev Neurosci. 2011; 34:413–440. [PubMed: 21469957]
18. Rossignol S, Frigon A, Barriere G, Martinez M, Barthelemy D, Bouyer L, Belanger M, Provencher J, Chau C, Brustein E, et al. Chapter 16--spinal plasticity in the recovery of locomotion. Prog Brain Res. 2011; 188:229–241. [PubMed: 21333814]
19. Segal RL, Wolf SL. Operant conditioning of spinal stretch reflexes in patients with spinal cord injuries. Exp Neurol. 1994; 130:202–213. [PubMed: 7867751]
20. Stein RB. Presynaptic inhibition in humans. Progress in Neurobiology. 1995; 47:533–544. [PubMed: 8787034]
21. Stein RB, Capaday C. The modulation of human reflexes during functional motor tasks. Trends Neurosci. 1988; 11:328–332. [PubMed: 2465639]
22. Stein RB, Yang JF, Belanger M, Pearson KG. Modification of reflexes in normal and abnormal movements. Prog Brain Res. 1993; 97:189–196. [PubMed: 8234745]
23. Taub E, Uswatte G, Pidikiti R. Constraint-Induced Movement Therapy: a new family of techniques with broad application to physical rehabilitation--a clinical review. J Rehabil Res Dev. 1999; 36:237–251. [PubMed: 10659807]
24. Thompson AK, Chen XY, Wolpaw JR. Acquisition of a simple motor skill: task-dependent adaptation plus long-term change in the human soleus H-reflex. J Neurosci. 2009; 29:5784–5792. [PubMed: 19420246]
25. Thompson AK, Chen XY, Wolpaw JR. Soleus H-reflex operant conditioning changes the H-reflex recruitment curve. Muscle Nerve. 2013; 47:539–544. [PubMed: 23281107]
26. Thompson AK, Estabrooks KL, Chong S, Stein RB. Spinal reflexes in ankle flexor and extensor muscles after chronic central nervous system lesions and functional electrical stimulation. Neurorehabil Neural Repair. 2009; 23:133–142. [PubMed: 19023139]
27. Thompson AK, Pomerantz FR, Wolpaw JR. Operant conditioning of a spinal reflex can improve locomotion after spinal cord injury in humans. J Neurosci. 2013; 33:2365–2375. [PubMed: 23392666]
28. Wernig A, Nanassy A, Muller S. Laufband (LB) therapy in spinal cord lesioned persons. Prog Brain Res. 2000; 128:89–97. [PubMed: 11105671]
29. Wolf SL, Winstein CJ, Miller JP, Taub E, Uswatte G, Morris D, Giuliani C, Light KE, Nichols-Larsen D. Effect of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke: the EXCITE randomized clinical trial. Jama. 2006; 296:2095–2104. [PubMed: 17077374]
30. Wolpaw JR. The complex structure of a simple memory. Trends Neurosci. 1997; 20:588–594. [PubMed: 9416673]

31. Wolpaw JR. Spinal cord plasticity in acquisition and maintenance of motor skills. Acta Physiol (Oxf). 2007; 189:155–169. [PubMed: 17250566]

32. Wolpaw JR. What can the spinal cord teach us about learning and memory? Neuroscientist. 2010; 16:532–549. [PubMed: 20889964]

33. Wolpaw JR, Tennissen AM. Activity-dependent spinal cord plasticity in health and disease. Ann Rev Neurosci. 2001; 24:807–843. [PubMed: 11520919]

34. Zehr EP. Training-induced adaptive plasticity in human somatosensory reflex pathways. J Appl Physiol. 2006; 101:1783–1794. [PubMed: 16809627]

35. Zehr EP, Stein RB. What functions do reflexes serve during human locomotion? Progress in Neurobiology. 1999; 58:185–205. [PubMed: 10338359]

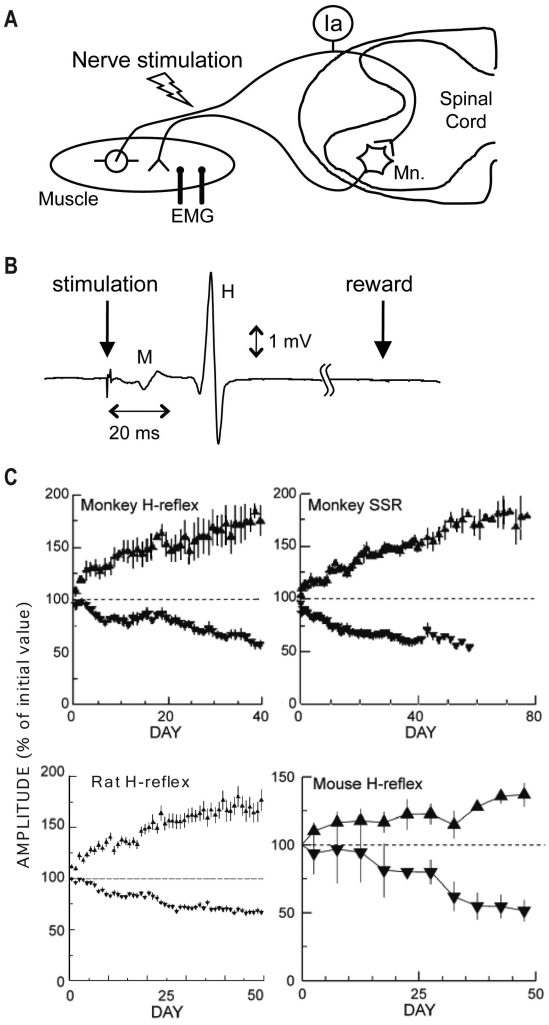

Figure 1.

A: Main pathway of the spinal stretch reflex (SSR) and its electrical analog, the H-reflex. Excitation of the Ia and Ib afferents (and possibly large group II and cutaneous afferents) activates the motoneurons innervating the same muscle and its synergists. If the afferents are excited by muscle stretch, the response is the SSR. If the afferents are excited by electrical stimulation, the response is the H-reflex. Although the pathway is entirely spinal, it is strongly influenced by supraspinal activity. B: Typical example of a soleus H-reflex trial in a human subject. In each conditioning trial, when the absolute value of soleus EMG remains within a specified range for 2 s, a stimulus to the tibial nerve just above M-wave threshold elicits the M-wave and the H-reflex. Visual feedback on the size of reflex (i.e., reward/no reward, depending on whether the reflex satisfies the size criterion) is provided 200 ms after the stimulus. C: Operant up- and down-conditioning of a spinal reflex in different animal models (top left: triceps surae H-reflex in monkeys; top right: biceps brachii spinal stretch reflex (SSR) in monkeys; bottom left: soleus H-reflex in rats; bottom right: triceps surae H-reflex in mice).

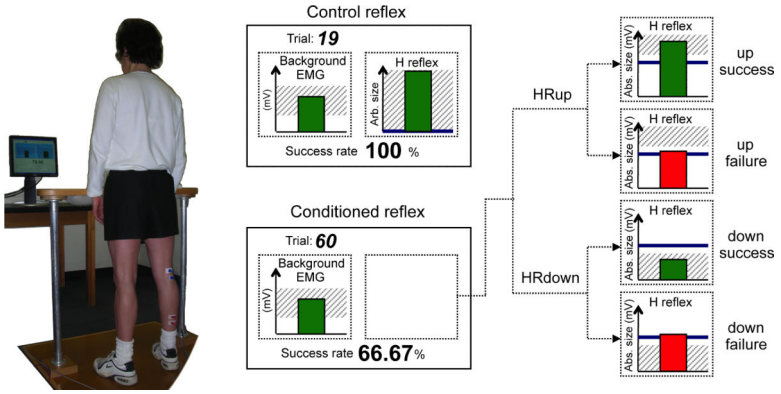

Figure 2.

Soleus H-reflex conditioning in human subjects. The subject maintains a natural standing posture facing a computer screen that displays the current level of soleus EMG in relation to a specified range. The ongoing soleus EMG (i.e., background) activity is shown on the left graph. When the background remains within the target (shaded) range for at least 2 sec, tibial nerve stimulation elicits a threshold M-wave and an H-reflex. In the right graph, the thick horizontal line indicates the subject's average H-reflex size for the baseline sessions (i.e., presented here as the mean rectified value of soleus EMG during the H-reflex interval (typically 30-45 ms after stimulus)). The right graph also has a shaded area indicating the range of H-reflex sizes that satisfy the reward criterion. In each reflex conditioning trial, a bar showing H-reflex size for that trial appears 200 ms after the stimulus. The bar is green if its height is within the shaded area (i.e., if H-reflex size satisfied the reward criterion), and the trial is counted as a success. If the height of the bar exceeds (HRdown) or does not reach (HRup) this range, the bar is red and the trial is counted as a failure. The criterion is based on the H-reflexes of the previous block of trials. In each conditioning session, the criterion value for the first block of 75 conditioning trials is determined based on the immediately preceding 20 control reflexes. The criterion values for the second and third conditioning blocks are based on the reflexes of the immediately preceding 75-trial block. [Adapted from (24).]

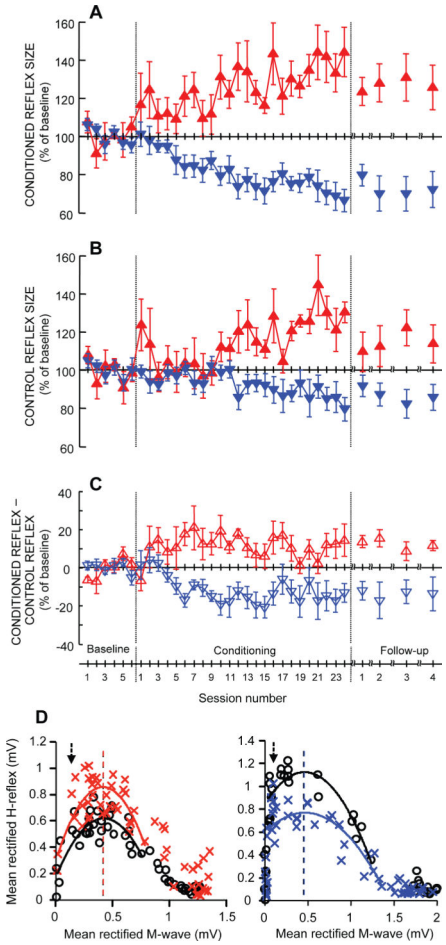

Figure 3.

Humans can change H-reflex size in response to an operant conditioning protocol. A: Average conditioned H-reflex size (±SE) for 6 successful HRup and 8 successful HRdown subjects for baseline, conditioning, and follow-up (12, 30, 60, and 90 days after the end of conditioning) sessions. B: Average control H-reflex size. C: Average of conditioning H-reflex size minus control H-reflex size. As in animals, H-reflex size gradually increases in the HRup subjects (upward triangles) and decreases in the HRdown subjects (downward triangles) over the course of the conditioning period. The final change (A) consists of task-dependent adaptation (C) plus long-term plasticity (B). See text for discussion. (Reprinted from (24). Copyright © 2009 Society for Neuroscience. Used with permission.) D: Average H-reflex recruitment curves for the 6 baseline sessions (o) and the last 6 conditioning sessions (x) of an HRup subject (left) and an HRdown subject (right). H-reflexes are plotted against the sizes of the accompanying M-waves. Second-order polynomial curves are fitted from the M-wave threshold to 50-70% Hmax of the down slope so that Hmax can be calculated for each curve (vertical lines). The arrow indicates the stimulus level used by the conditioning protocol (i.e., the M-wave size targeted by the protocol). In the subject of the left panel (as in 5 of the 6 HRup subjects), the recruitment curve is broad, the entire curve is elevated by conditioning, and the stimulus level that produces Hmax does not change. In the subject of the right panel (as in 3 of the 6 HRdown subjects), the entire recruitment curve is

depressed by conditioning, and the stimulus level that produces Hmax does not change. (In the other HRup subject, the entire curve was shifted to the left; and in the other 3 HRdown subjects, the entire curve was shifted to the right.) (Reprinted from (25). Copyright © 2013 Wiley Periodicals, Inc. Used with permission.)

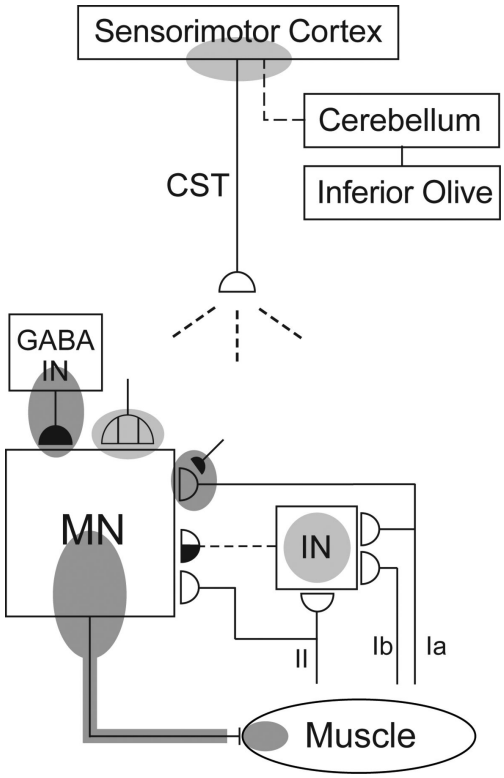

Figure 4.

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 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. Dashed pathways imply the possibility of intervening spinal interneurons. The monosynaptic and probably oligosynaptic SSR/H-reflex pathway from groups Ia, II, and Ib afferents to the motoneuron is shown. Definite (dark shading) or probable (light grey 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 groups I and II inhibition or excitation to the motoneuron; and sensorimotor cortex. The essential roles of the corticospinal tract (which originates largely in sensorimotor cortex), of cerebellar output to cortex, and of inferior olive output to cerebellum 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 and the inferior olive. [Adapted from (32).]

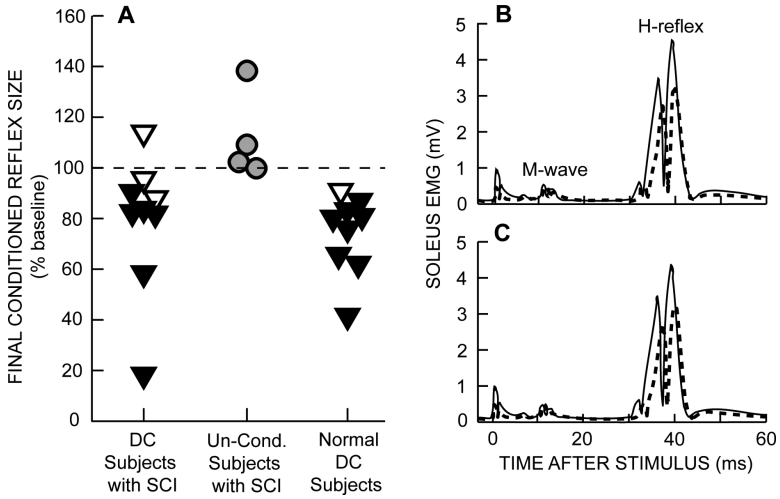

Figure 5.

A: Final conditioned H-reflex sizes (i.e., average for the last 3 conditioning sessions) for individual Down-Conditioning (DC) and Unconditioned (Un-Cond.) subjects. The filled triangles represent the DC subjects whose conditioned H-reflexes for the last 6 conditioning sessions were significantly less than their H-reflexes for the 6 Baseline sessions. The open triangles represent the DC subjects in whom the H-reflex did not decrease significantly. B and C: Average conditioned (B) and control (C) H-reflexes for a baseline session (solid) and the last conditioning session (dashed) from a DC subject with SCI in whom the H-reflex decreased significantly. Both conditioned and control H-reflexes are smaller after 30 conditioning sessions. (Reprinted from (24, 27). Copyright © 2009, 2013 Society for Neuroscience. Used with permission.)

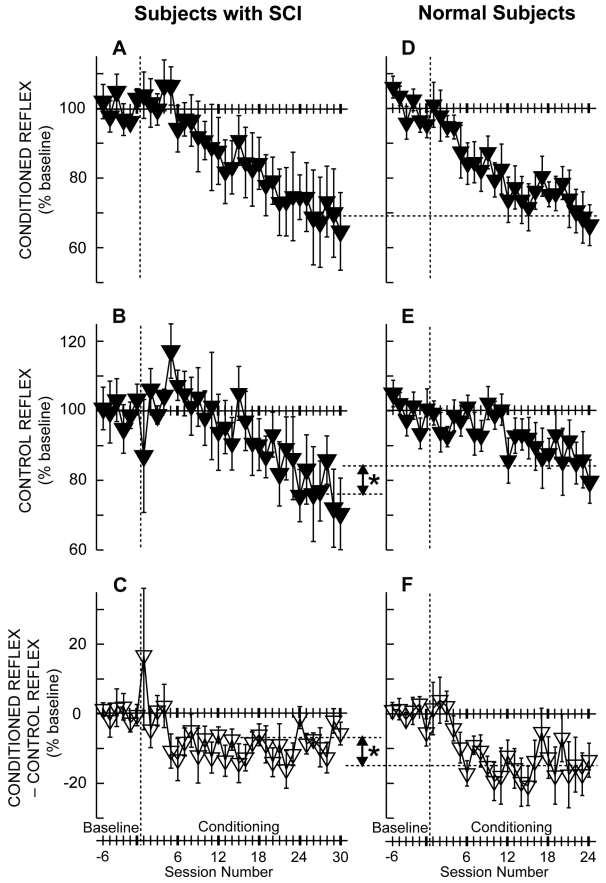

Figure 6.

Average (±SE) H-reflexes for baseline and conditioning sessions for Down-Conditioning (DC) subjects with SCI (A, B, and C, N=6, (27)) and for normal subjects (D, E, and F, N=8, (24)) in whom the H-reflex decreased significantly. A and D: Average conditioned H-reflex size. B and E: Average control H-reflex size (i.e., long-term plasticity (see (24) for details). C and F: Average of conditioned H-reflex size minus control H-reflex size (i.e., task-dependent adaptation (see (24) for details)). In the subjects with SCI, the conditioned H-reflex decreases to 69% of the baseline value over the 30 conditioning sessions (A). This decrease consists of a relatively small task-dependent adaptation (-7%, C) and a relatively large across-session control reflex decrease (-24%, B). In the subjects without disability (24), the conditioned H-reflex also decreases to 69% of the baseline value over 24 Conditioning sessions (D). This decrease consists of a relatively large task-dependent adaptation (-15%, F) and a relatively small across-session control reflex decrease (-16%, E). The asterisks between B and E and between C and F indicate significant differences ($p<0.01$) between subjects with SCI and normal subjects in final control H-reflex value and in task-dependent adaptation, respectively. Task-dependent adaptation is greater in the normal subjects, while change in the control H-reflex is greater in the subjects with SCI. (See (27) for discussion of this difference.)

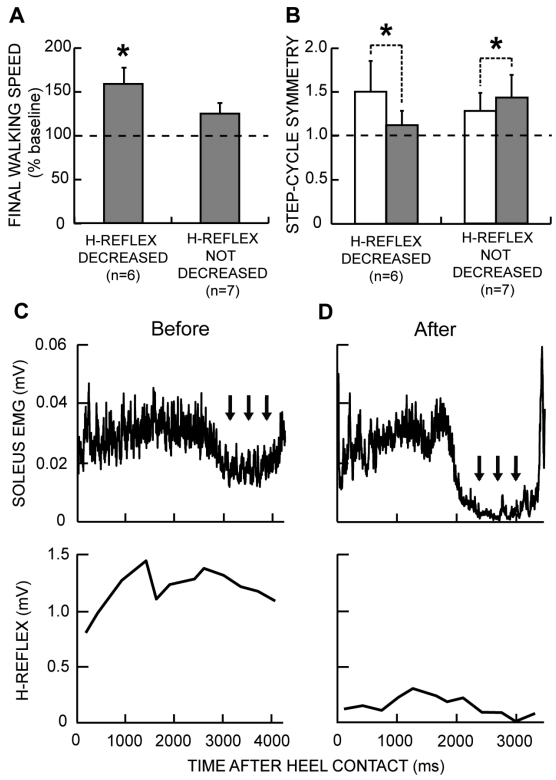

Figure 7.

A: Average (±SE) 10-m walking speeds after the 30 conditioning or control sessions (in % of baseline speed) for subjects with SCI in whom the H-reflex did or did not decrease significantly. B: Step-cycle symmetry before (open bars) and after (shaded bars) the 30 conditioning or control sessions for subjects with SCI in whom the H-reflex did or did not decrease significantly. Symmetry is measured as the ratio of the time between the nonconditioned leg's foot contact (nFC) and the conditioned (or simply stimulated in the case of UC subjects, and initially more affected) leg's foot contact (cFC) to the time between cFC and nFC. A ratio of 1 indicates a symmetrical gait. Initially, the ratio is >1. After the 30 conditioning or control sessions, the ratio has decreased toward 1 in the subjects in whom the H-reflex decreased, while it has increased slightly in the subjects in whom the H-reflex did not decrease. C and D, Rectified soleus EMG and locomotor H-reflex size over the step cycle before and after successful H-reflex down-conditioning in a subject with SCI. Successful conditioning results in better soleus EMG modulation: the abnormal tonic activity during the swing phase is almost totally gone after conditioning. In addition, the locomotor H-reflex is greatly decreased and better modulated after conditioning (i.e., it is lowest during the swing phase). (Reprinted from (27). Copyright © 2013 Society for Neuroscience. Used with permission.)