

Restoring Walking after Spinal Cord Injury: Operant Conditioning of Spinal Reflexes Can Help

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Abstract

People with incomplete spinal cord injury (SCI) frequently suffer motor disabilities due to spasticity and poor muscle control, even after conventional therapy. Abnormal spinal reflex activity often contributes to these problems. Operant conditioning of spinal reflexes, which can target plasticity to specific reflex pathways, can enhance recovery. In rats in which a right lateral column lesion had weakened right stance and produced an asymmetrical gait, up-conditioning of the right soleus H-reflex, which increased muscle spindle afferent excitation of soleus, strengthened right stance and eliminated the asymmetry. In people with hyperreflexia due to incomplete SCI, down-conditioning of the soleus H-reflex improved walking speed and symmetry. Furthermore, modulation of electromyographic activity during walking improved bilaterally, indicating that a protocol that targets plasticity to a specific pathway can trigger widespread plasticity that improves recovery far beyond that attributable to the change in the targeted pathway. These improvements were apparent to people in their daily lives. They reported walking faster and farther, and noted less spasticity and better balance. Operant conditioning protocols could be developed to modify other spinal reflexes or corticospinal connections; and could be combined with other therapies to enhance recovery in people with SCI or other neuromuscular disorders.

Keywords

spinal cord injury, locomotion, spinal reflexes, spinal cord plasticity, learning

Introduction

People with incomplete spinal cord injury (SCI) often have substantial disabilities, even after completing conventional therapy. Common movement problems in individuals with chronic SCI, such as spasticity and weak voluntary muscle contraction, are thought to result from a combination of disrupted supraspinal connections, altered activity of spinal reflex pathways, and altered muscle properties (including disuse muscle atrophy and contracture) (Dietz and Sinkjaer 2007; Hultborn 2003). Thus, reducing abnormalities in one or more of these components may improve functional recovery. In this article, we focus on spinal reflex abnormalities and on evidence that operant conditioning protocols that target spinal reflex pathways may enhance restoration of motor function after SCI. We first review the spinal reflex abnormalities that contribute to movement problems. We then introduce the operant conditioning methodology that can induce targeted plasticity in a selected reflex pathway and summarize current understanding of the substrates of conditioning-induced reflex change. Finally, we highlight the remarkably broad beneficial effects of changing a

specific reflex pathway; and we explicate these effects in terms of a new concept of the role of the spinal cord in motor function.

Spinal Reflex Abnormalities and Impaired Locomotion after Incomplete Spinal Cord Injury

Incomplete SCI disrupts supraspinal connections and often alters spinal reflex activity (Crone and others 2003;

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Stein and others 1993; Thompson and others 2009b; Yang and others 1991). Changes in spinal reflex pathways contribute to the most common and disabling locomotor problems, such as clonus, foot drop, and limited joint motion. For instance, ankle dorsiflexion during walking is often weakened after SCI due to the loss of normal corticospinal activation (Barthelemy and others 2010; Davey and others 1999). Exaggerated stretch reflexes in extensor muscles may counteract the remaining dorsiflexion and exacerbate foot drop (Knutsson 1981; Yang and others 1991). Furthermore, hyperactive stretch reflex pathways may limit joint motion (Hornby and others 2006) and may also lead to clonus (Corcos and others 1986; Hidler and Rymer 1999; Wallace and others 2012; Yang and others 1991).

Normally, spinal reflexes are appropriately modulated according to the current motor task. For instance, soleus H-reflex gain decreases greatly from standing to walking (see Fig. 1A) to running (Capaday and Stein 1986, 1987; Stein and Capaday 1988), which prevents saturation of motor output and the reflex feedback loop (Capaday and Stein 1987). However, in people with SCI, Ia excitation is heightened (Knutsson and others 1973; Mailis and Ashby 1990) and task-dependent H-reflex modulation is greatly diminished or absent (Boorman and others 1996; Thompson and others 2009b). Furthermore, group Ib inhibition of the soleus by medial gastrocnemius nerve stimulation is impaired (Morita and others 2006), reciprocal and presynaptic inhibition are reduced (Ashby and Wiens 1989; Crone and others 2003; Knikou and Mummidisetty 2011; Morita and others 2001), and recurrent inhibition of the soleus is increased (Shefner and others 1992). Reflex abnormalities also exist in other muscles (Faist and others 1999). Alterations in motoneuron and interneuron properties also contribute to spastic reflex behaviors after SCI (Gorassini and others 2004; Heckman and others 2008; Hornby and others 2006; Hultborn 2003; Onushko and Schmit 2007). Altogether, these studies indicate that abnormal activity in spinal pathways contributes in multiple ways to motor impairments after SCI (Dietz and Sinkjaer 2007; Hultborn 2003; Stein and others 1993; Yang and others 1991).

During walking, soleus muscle activity is dynamically modulated; it increases from heel-contact to push-off, at which time the EMG level peaks, and then drops down to almost no activity and remains quiet for the entire swing phase (Fig. 1C). Different reflex pathways are thought to contribute to different parts of the soleus electromyographic (EMG) burst that occurs in the stance phase of the step-cycle. During stance, the ankle undergoes a natural dorsiflexion that stretches the soleus muscle, and input from group Ia and II afferents contributes to the soleus burst (Mazzaro and others 2006; Mazzaro and others 2005; Sinkjaer and others 1996). In addition, input from

group Ib afferents enhances the latter part of the burst (Grey and others 2007; Mazzaro and others 2006). The fact that these spinal pathways contribute to normal locomotor EMG activity helps to explain why the reflex abnormalities produced by SCI impair locomotion.

After SCI, excitation of motoneurons by muscle spindle afferents is enhanced and task-dependent H-reflex modulation is often impaired (Knutsson and others 1973; Mailis and Ashby 1990; Thompson and others 2009b). Figure 1 illustrates these abnormalities and the associated impairments in locomotor EMG activity. The normal increase in H-reflex size with increasing background EMG activity during standing is diminished; and the task-dependent modulation of reflex gain from standing to walking that normally prevents saturation of motor output and the reflex feedback loop is lost (Boorman and others 1996; Thompson and others 2009b) (Fig. 1A: normal subject data vs. data from subjects with SCI). Reflex modulation over the step-cycle may also be lost (Fig. 1B), probably due to saturation of the reflex loop (Stein and others 1993; Yang and others 1991). Normally, the soleus stretch reflex (and H-reflex) pathways are active during the stance phase to assist force production, and they are suppressed during the swing phase to prevent foot drop (Capaday and Stein 1986; Schneider and others 2000; Sinkjaer and others 1999). Both overall increase in reflex size and lack of phase-dependent reflex modulation characterize the reflex abnormalities in people with SCI (Boorman and others 1996; Thompson and others 2009b; Yang and others 1991).

In subjects with SCI, the hyperactive reflex pathways and the loss of modulation over the step-cycle are associated with abnormal patterns of soleus locomotor EMG activity, such as activity during the swing phase (e.g., Fig. 1C, right panel). Furthermore, the unsuppressed soleus reflex activity from the swing to early stance may suppress tibialis anterior (i.e., ankle dorsiflexor) activation and thereby contribute to foot drop (e.g., Fig. 1D). The hyperactive soleus stretch reflex pathways also contribute to the clonic activity in soleus that is commonly observed during the early stance phase of the step-cycle (Yang and others 1991). These problems may be further exaggerated by abnormalities in other spinal pathways, including those of reciprocal inhibition (Ashby and Wiens 1989; Boorman and others 1996; Crone and others 2003; Knikou and Mummidisetty 2011; Thompson and others 2009b), presynaptic inhibition (Morita and others 2001), and/or cutaneous reflexes (Frigon and others 2009; Knikou 2007).

Treating Reflex Abnormalities after Spinal Cord Injury

Because the spinal reflex abnormalities associated with incomplete SCI impair locomotion and other important functions, their amelioration continues to be a major

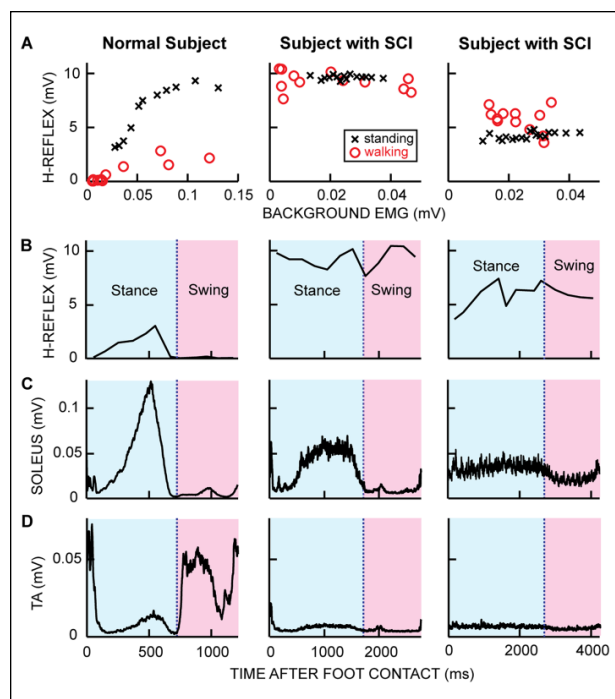


Figure 1. Soleus H-reflex during standing and walking, soleus and tibialis anterior (TA) electromyographic (EMG) activity and soleus H-reflex size over the step-cycle in a neurologically normal subject and in two subjects with chronic incomplete spinal cord injury (SCI). (A) Soleus H-reflex sizes during standing and walking in each of 12 equally spaced step-cycle bins versus soleus EMG activity. Each standing H-reflex symbol (x) is the average of four responses and each walking H-reflex symbol (o) is the average of 5 to 10 responses. M-wave sizes are maintained the same within and between tasks. In the normal subjects, the H-reflex at a specific EMG level is clearly smaller during walking than during standing (Capaday and Stein 1986), whereas in subjects with chronic SCI, this task-dependent modulation of H-reflex size between standing and walking is impaired; and H-reflex size does not increase with background EMG level in standing or walking. (B) Soleus H-reflex modulation during walking. In the normal subject, the pattern is similar to the soleus EMG pattern (C). In the subjects with SCI (middle and right), H-reflex modulation across the step-cycle is minimal, and hyperactivity of the H-reflex pathway probably contributes to the abnormally low TA activity during the swing phase (D) and to the resulting foot drop. (C) Soleus EMG during walking. In the normal subject, soleus EMG activity gradually increases from heel contact to push off, then falls to near zero and remains low for the entire swing phase. In figure subjects with SCI, soleus EMG activity may (middle) or may not (right) be normally modulated. In the subject on the right column, the soleus remains active during the swing phase. (D) TA EMG activity during walking. In the normal subject, TA activity typically shows two distinct peaks: one in the early swing phase and another during the swing-stance transition. In subjects with SCI (middle and right), TA activity is often minimal throughout the step-cycle.

therapeutic goal. Current therapies are mainly pharmacological and they seek to weaken muscles or reflexes (e.g., botulinum toxin or baclofen). They are nonspecific in that they affect muscle activity and/or reflex pathways in general and they may have undesirable side effects (Dario and others 2004; Dario and Tomei 2004; Sheean 2006; Ward 2008). Repetitive stimulation of peripheral nerve (i.e., transcutaneous electrical nerve stimulation or functional electrical stimulation) or cortex (repetitive transcranial magnetic stimulation) may be effective in reducing spasticity (Goulet and others 1996; Mori and others 2009; Thompson and others 2011). The responsible mechanisms and the extent of the therapeutic effects are not yet clear.

Novel therapies that can target specific reflex pathways and can strengthen or weaken them as appropriate could substantially improve functional recovery after SCI. Recent studies suggest that operant conditioning of spinal reflexes, which was first developed as a basic science model 30 years ago, can provide a specific, flexible, and clinically practical new approach to addressing the spinal reflex abnormalities associated with incomplete SCI. In rats in which a right lateral column lesion had weakened right stance and produced an asymmetrical gait (i.e., the rats limped), up-conditioning of the right soleus H-reflex, which increased the muscle spindle afferent contribution to the soleus stance burst, strengthened right stance, and eliminated the asymmetry (Y. Chen and others 2006). And, in people in whom an incomplete SCI had produced spasticity that impaired locomotion, operantly conditioned decrease in the soleus H-reflex reduced spasticity and improved locomotor speed and symmetry (Thompson and others 2013c). The next sections review spinal reflex conditioning and the complex plasticity that underlies it, describe its impact on locomotion after SCI, consider the mechanisms of its surprisingly broad beneficial effects, and discuss its future therapeutic possibilities.

Operant Conditioning of Spinal Reflexes

The first reflex operant conditioning protocol was designed to change the spinal stretch reflex in the monkey biceps muscle (Wolpaw and others 1983). This protocol had three key features: (1) it required maintaining a certain level of background (prestimulus) EMG in the target muscle; (2) it based reward on the size of the reflex as measured by EMG; and (3) the reward contingency (i.e., whether larger or smaller reflexes were rewarded) remained the same over days and weeks. The protocol sought to induce and maintain a long-term change in

descending influence over the spinal reflex pathway, and thus to produce plasticity in the pathway (see Wolpaw 1997 for review). These three features have been preserved in all subsequent versions of the protocol, across different species (i.e., monkey, rat, human, mouse), muscles (i.e., biceps brachii, triceps surae, soleus), and reflexes (i.e., spinal stretch reflex, H-reflex, reciprocal inhibition) (Thompson and Wolpaw 2014a).

Spinal Reflex Conditioning in Rats

At present, the standard laboratory protocol is operant conditioning of the soleus H-reflex in the rat (Chen and Wolpaw 1995). This protocol is illustrated in Figure 2A to 2C. A Sprague-Dawley 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, a flexible tether, and a commutator to an EMG amplifier and an electrical simulator. Soleus EMG is monitored continuously (24 hours a day) in the freely moving animal. Whenever the absolute value of soleus EMG remains within a specified range for a random varying 2.3- to 2.7-second period, a stimulus through the nerve cuff elicits the M-wave just above threshold and the H-reflex. In the course of its normal activity, the rat usually provides 2500 to 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 (i.e., control) 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 size remain constant throughout. As shown in Figure 2B and 2C, chronic exposure to the up- or down-conditioning mode gradually changes the size of the reflex in the correct direction. Successful conditioning (i.e., >20% change in the correct direction; Chen and Wolpaw 1995; Wolpaw and others 1993) occurs in 75% to 80% of the animals. The other 20% to 25% of the rats, in which the H-reflex remains within 20% of its initial value, constitute a useful control population for mechanistic studies.

Spinal Reflex Conditioning in Humans

Figure 2D to 2G shows the soleus H-reflex conditioning protocol for humans (Thompson and others 2009a). It has the three key features described above. At the same time, it differs from the animal protocols in several ways: (1) conditioning occurs in discrete 1-hr sessions of 225 conditioning trials each at a rate of 3/week over 8 to 10 weeks (thus people complete only 3% to 5% as

many trials as the rats that are continuously exposed to conditioning over 50 days); (2) the EMG recording and nerve stimulating electrodes are superficial rather than implanted; (3) the reward is visual feedback rather than a food pellet; and (4) each session begins with 20 control trials in which the subject is not asked to change the reflex and receives no feedback as to reflex size. The standard format comprises 6 baseline and then 24 (or 30) conditioning sessions at a rate of three per week. In each trial, the soleus H-reflex is elicited while the subject maintains a natural standing posture and a predetermined level of soleus background EMG (Fig. 2D). M-wave size is kept constant within and across the sessions. In each baseline session, 3 blocks of 75 control H-reflexes each (i.e., 225 total) are elicited (Fig. 2E). In each conditioning or follow-up session, 20 control H-reflexes are elicited as in the baseline sessions and then 3 blocks of 75 conditioned H-reflexes (i.e., 225 total) are elicited. In these conditioned H-reflex trials, the subject is asked to increase (up-conditioning [HRup]) or decrease (down-conditioning [HRdown]) the H-reflex and is given immediate visual feedback as to whether the H-reflex was larger (HRup) or smaller (HRdown) than a criterion value. Satisfying the criterion on more than a specific percent of the trials earns an additional monetary reward. Background EMG and M-wave size are kept stable throughout data collection.

In the first H-reflex conditioning study in normal humans (Thompson and others 2009a), H-reflex size gradually increased to 140% of baseline in 6 of 8 HRup subjects and decreased to 69% of baseline in 8 of 9 HRdown subjects (Fig. 2F and 3B). In these subjects, the conditioned H-reflex change was the sum of within-session change (i.e., task-dependent adaptation, measured as the within-session difference in size between the control and conditioned H-reflexes) and across-session change (i.e., long-term change, measured as the across-session change in control H-reflex size) (Fig. 3B). Task-dependent adaptation appeared within 4 to 6 sessions and then persisted unchanged, while long-term change began after 10 to 12 sessions and increased gradually thereafter. (See Thompson and others 2009a for full discussion of task-dependent adaptation and long-term change.) This study showed that people performing only 3% to 5% as many trials as the rats can change reflex size nearly as much. The success rate of 82% (14 of 17 subjects changed H-reflex size significantly in the correct direction) was also similar to that of animals (Thompson and others 2009a; Wolpaw 1997). In addition, this study showed that exposure to the reflex operant conditioning paradigm over several months induced both short-term adaptation and long-term plasticity in spinal reflex pathways. This long-term plasticity, a lasting change in the reflex pathway

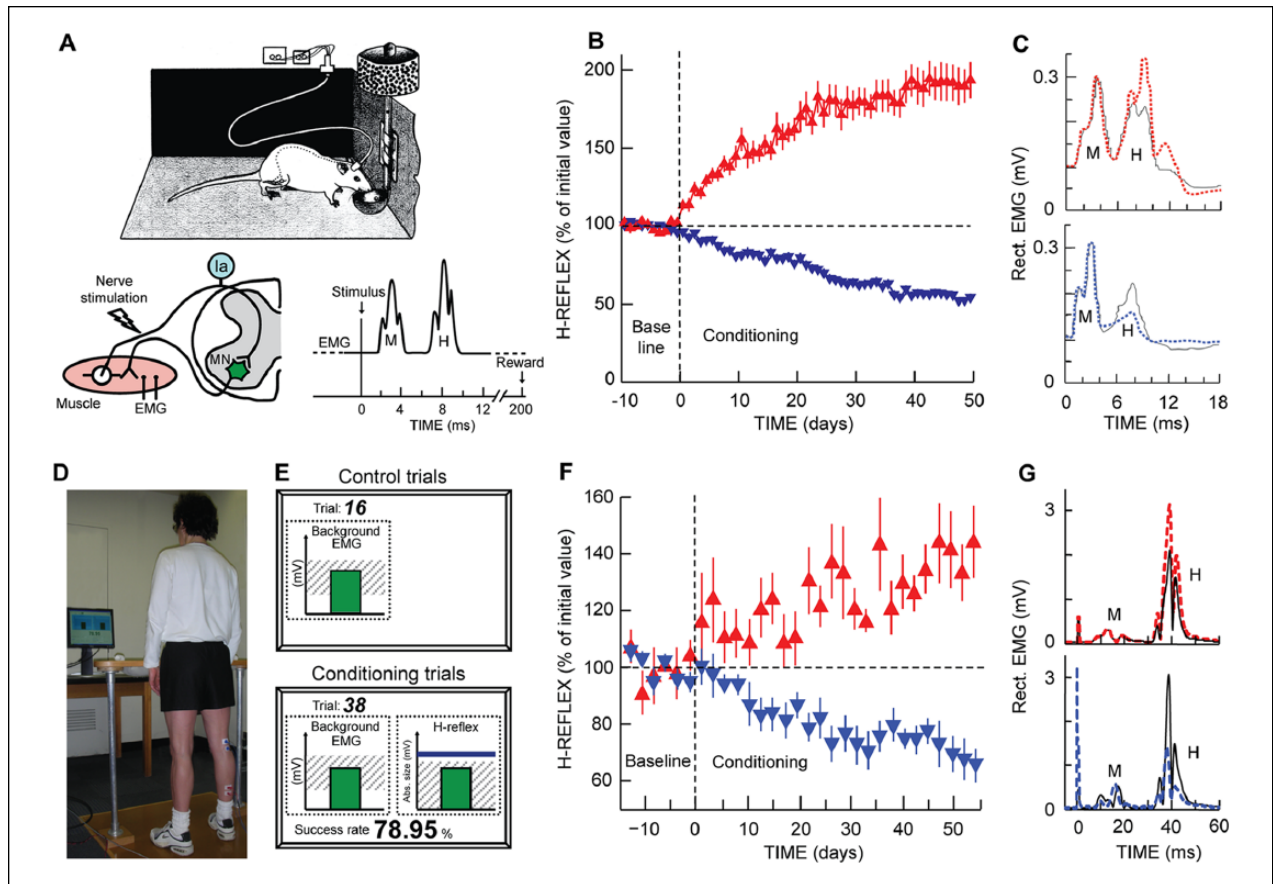


Figure 2. H-reflex operant conditioning in rats (A-C) and humans (D-G). **A:** The soleus H-reflex is elicited in a rat with chronically implanted electromyography (EMG) electrodes and a tibial nerve cuff. Whenever the absolute value of soleus EMG activity stays in a specified range for a 2.3- to 2.7-second period, tibial nerve stimulation through the cuff elicits an M-wave just above threshold and an H-reflex. 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, the rat is exposed to the up-conditioning (HRup) or down-conditioning (HRdown) mode, in which a food-pellet reward occurs 200 ms after the stimulation whenever the H-reflex is above (HRup) or below (HRdown) a criterion value. **(B)** Average (\pm standard error of the mean [SEM]) daily H-reflex sizes for 59 successful HRup rats (red upward triangles) and 81 successful HRdown rats (blue downward triangles). **(C)** Average absolute value of poststimulus EMG activity for representative days from an HRup rat (top) and an HRdown rat (bottom) in the control mode (solid) and near the end of HRup or HRdown conditioning (dashed) (updated from Wolpaw 1997). **(D-G)** The subject maintains a natural standing posture and a correct level of soleus EMG activity with the aid of a visual feedback screen (D and E) that shows the current absolute value of soleus EMG activity in relation to a specified range. Whenever the absolute value of soleus EMG activity stays in this range for several sec, tibial nerve stimulation elicits an M-wave just above threshold and an H-reflex. For the first 6 sessions (i.e., baseline sessions, day -14 to day 0), the subject is exposed to the control mode, in which the H-reflex is simply measured to determine its initial size. For the next 24 sessions (i.e., conditioning sessions, days 0 to 56, 3 sessions/week), the subject is exposed to the HRup or HRdown conditioning mode, in which, after each conditioning trial, the screen provides immediate feedback as to whether the H-reflex was above (HRup) or below (HRdown (shown on screen)) a criterion value **(E)**. The person completes 225 conditioning trials per session. **(F)** Average (\pm SEM) daily H-reflex sizes for 6 successful HRup people (red upward triangles) and 8 successful HRdown people (blue downward triangles). **(G)** Average peristimulus EMG activity from a HRup subject (top) and an HRdown subject (bottom) for a baseline session (i.e., control mode) (solid) and for the last HRup or HRdown conditioning session (dashed). From Thompson and others (2009a).

that persists outside of the conditioning paradigm, suggests that reflex conditioning could be of use therapeutically (Thompson and others 2009a; Thompson and others 2013a). Can reflex conditioning protocols induce

and guide such long-term plasticity so as to re-educate abnormally functioning spinal reflex pathways and thereby alleviate motor disabilities associated with incomplete spinal cord injuries?

The Plasticity Associated with H-Reflex Conditioning

Studies in monkeys and rats show that H-reflex conditioning is associated with plasticity at multiple sites in the spinal cord and brain (Thompson and Wolpaw 2014b; Wolpaw 2010) for review). Figure 7 summarizes current knowledge of this plasticity. In the spinal cord, successful conditioning is accompanied by changes in motoneuron properties (e.g., firing threshold and axonal conduction velocity), in GABAergic terminals and several other terminal populations on the motoneuron, and in spinal interneurons. Plasticity occurs in the brain as well, most probably in sensorimotor cortex and cerebellum. H-reflex conditioning requires the corticospinal tract; other major descending and ascending pathways are not essential. The picture that is emerging is of a hierarchy of plasticity in which the reward contingency produces plasticity in the brain that guides and maintains the plasticity in the spinal cord that is directly responsible for the conditioned H-reflex change (Thompson and Wolpaw 2014b; Wolpaw 2010).

Operant Conditioning of the H-Reflex after Spinal Cord Injury

Spinal Reflex Conditioning in Rats with Spinal Cord Injury

The hypothesis that appropriate operant conditioning of a spinal reflex can ameliorate the motor disability after incomplete SCI was first tested in rats in which a right lateral column lesion had weakened right stance and produced an asymmetrical gait (Y. Chen and others 2006). The right soleus H-reflex was up-conditioned in order to increase the muscle spindle afferent contribution to the soleus stance burst (Bennett and others 1996; Stein and others 2000). The results were clear and impressive. In successfully up-conditioned rats the H-reflex increased to 212% of its initial value (comparable to the increase in normal rats; Chen and others 2005), the stance-phase H-reflex increased to 280%, and the right soleus stance burst amplitude increased to 158%. As a result, right stance was strengthened and the right/left asymmetry was eliminated; locomotion was improved significantly in these rats with partial SCI (Y. Chen and others 2006). Locomotion did not improve in rats in which the H-reflex was simply measured but not conditioned (Y. Chen and others 2006).

Spinal Reflex Conditioning in Humans with Spinal Cord Injury

This evidence for therapeutic efficacy in rats (Y. Chen and others 2006), together with the successful development of

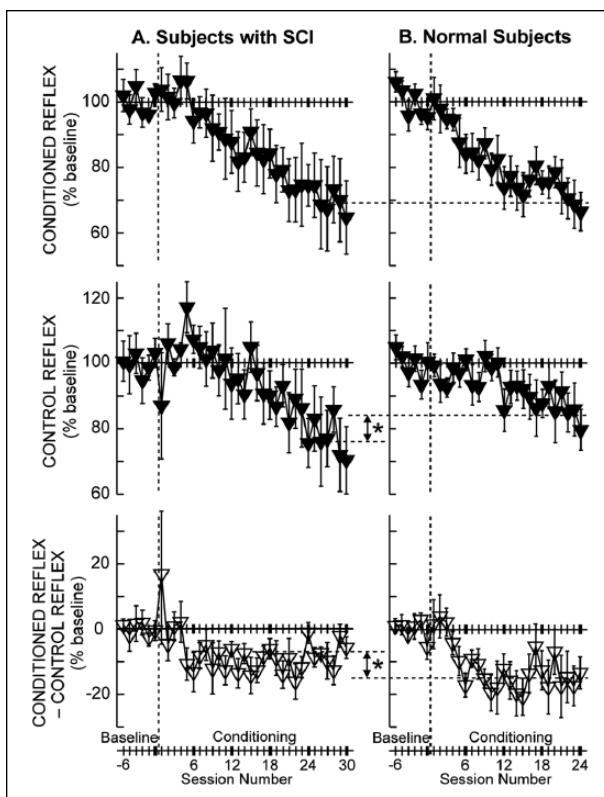


Figure 3. Average (\pm standard error [SE]) H-reflexes for baseline and conditioning sessions for down-conditioning subjects with SCI (A, N = 6; Thompson and others 2013c) and for normal subjects (B, N = 8; Thompson and others 2009a) in whom the H-reflex decreased significantly. (Top) Average conditioned H-reflex size. (Middle) Average control H-reflex size (i.e., long-term plasticity; see Thompson and others 2009a for details). (Bottom) Average of conditioned H-reflex size minus control H-reflex size (i.e., task-dependent adaptation; see Thompson and others 2009a for details). In the subjects with SCI (A), the conditioned H-reflex decreases to 69% of the baseline value over the 30 conditioning sessions. This decrease consists of a relatively small task-dependent adaptation (-7%) and a relatively large across-session control reflex decrease (-24%). In neurologically normal subjects (B), the conditioned H-reflex also decreases to 69% of the baseline value over 24 conditioning sessions. This decrease is the sum of a relatively large task-dependent adaptation (-15%) and a relatively small across-session control reflex decrease (-16%). The asterisks between (A) and (B) indicate significant differences ($P < 0.01$) between the groups in final control H-reflex value (middle) and in task-dependent adaptation (bottom).

the human H-reflex conditioning protocol (Thompson and others 2009a) and the evidence that it induced long-term plasticity in the human H-reflex pathway (Thompson and others 2009a; Thompson and others 2013a), encouraged an effort to determine whether H-reflex conditioning could improve locomotion in people. We studied individuals in whom an incomplete

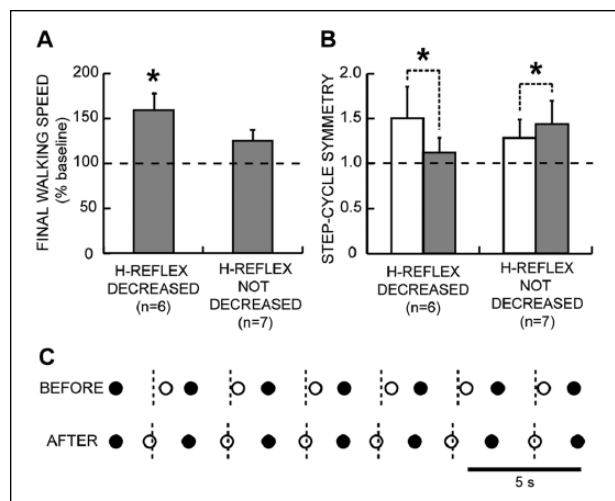


Figure 4. (A) Ten-meter walking speeds after the 30 conditioning or control sessions (mean \pm standard error [SE] % of baseline speed) for subjects with spinal cord injury (SCI) in whom the H-reflex did or did not decrease significantly. (B) Step-cycle symmetry before (open bars) and after (shaded bars) after 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 control subjects) and initially more impaired 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) Successive step-cycles before and after conditioning from a subject in whom the H-reflex decreased. Each nFC (\bullet) and cFC (\circ) is shown. Short vertical dashed lines mark the midpoints between nFCs (i.e., midpoints of the step-cycle), which is when cFC should occur. Before H-reflex conditioning, cFC is too late; after successful conditioning, it is on time.

spinal cord injury had produced spasticity that impaired locomotion. Given that each person displayed a hyperactive soleus H-reflex, we evaluated the therapeutic efficacy of down-conditioning the soleus H-reflex (Thompson and others 2013c).

Over 30 down-conditioning sessions, the soleus H-reflex decreased in two-thirds of the subjects and remained smaller several months later. In the subjects in whom H-reflex decreased significantly, locomotion improved; walking speed increased and right-left symmetry improved (Fig. 4), with better EMG modulation across the step-cycle in the muscles of both legs. In these subjects, the H-reflex decrease was also evident during locomotion (i.e., 59% of initial value), which helped to explain the improved gait (e.g., Fig. 5). Furthermore, beginning about 5 weeks into the conditioning sessions,

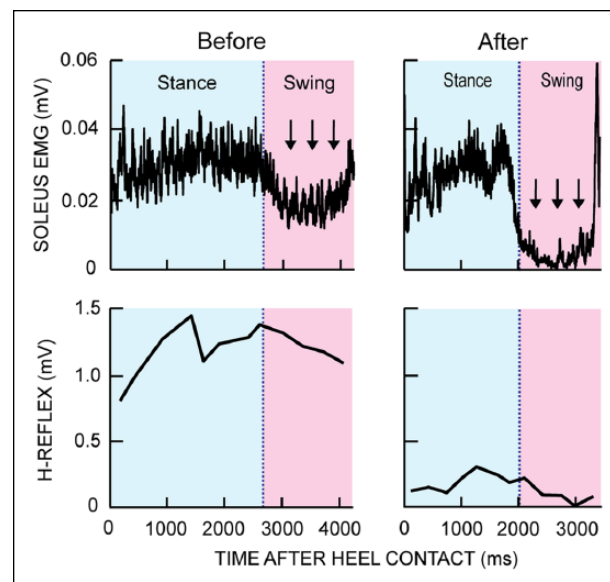


Figure 5. Rectified soleus electromyographic (EMG) activity and locomotor H-reflex size over the step-cycle before and after successful H-reflex down-conditioning in a subject with SCI. Successful conditioning results in better EMG and H-reflex modulation. The abnormal tonic EMG activity during the swing phase almost completely disappears after conditioning. The locomotor H-reflex becomes smaller and better modulated after conditioning (i.e., it is lowest during the swing phase). Note also that the step-cycle is shorter after conditioning, which translated to an increase in walking speed.

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. Locomotion did not improve in the subjects in whom H-reflex down-conditioning was not successful or in subjects in whom the H-reflex was simply measured over 30 sessions without conditioning. These first results in people with SCI, together with the rat study, suggest that operant conditioning of spinal reflexes can improve gait recovery after chronic incomplete SCI, and possibly in other disorders as well (e.g., Chen and others 2010).

Current understanding of the spinal cord plasticity associated with H-reflex down-conditioning provides some insight into the mechanisms that may underlie the locomotor improvement in people with SCI. In these individuals with spasticity due to SCI, motoneuron excitation from muscle spindle afferents is exaggerated (Knutsson and others 1973; Mailis and Ashby 1990), motoneuron and interneuron properties are altered (Gorassini and others 2004; Heckman and others 2008; Hornby and others 2006; Hultborn 2003; Onushko and Schmit 2007), and inhibitory interneuron activity is abnormal (Ashby and Wiens 1989; Boorman and others

1996; Crone and others 2003; Knikou and Mummidisetty 2011; Morita and others 2001; Thompson and others 2009b). H-reflex down-conditioning raises motoneuron firing threshold, slightly decreases the primary afferent EPSP, and markedly increases the number of identifiable GABAergic terminals on the motoneuron and the number of identifiable GABAergic interneurons in the ventral horn (reviewed in Wolpaw 2010). By counteracting the abnormalities associated with SCI, these effects may underlie the locomotor improvement produced by H-reflex down-conditioning.

Spinal Reflex Conditioning in Humans with Spinal Cord Injury Differs from That in Normal Humans

In data to date, the probability of successful conditioning and the magnitude of reflex change are comparable in people with or without incomplete SCI (Y. Chen and others 2006; Chen and others 2005; Thompson and others 2009a; Thompson and others 2013c). However, as Figure 3 shows, these two populations differ markedly in the proportions of task-dependent adaptation and long-term change in the final conditioned H-reflex (Thompson and others 2013c). Task-dependent adaptation (i.e., within-session change), which is thought to reflect immediate change in cortical influence (e.g., on presynaptic inhibition), is significantly greater in neurologically normal subjects than in subjects with SCI (-15% vs. -7%; Figure 3, bottom). This difference may be due to SCI-related reduction in cortical influence due to damage to the corticospinal tract, the supraspinal connection principally responsible for H-reflex conditioning (reviewed in Thompson and Wolpaw 2014b; Wolpaw 2010). Such damage may also account for the slightly slower course of H-reflex decrease (i.e., over 30 sessions vs. 24 sessions in normal subjects). In contrast, long-term H-reflex change (i.e., across-session change), which is thought to reflect spinal cord plasticity, is significantly greater in subjects with SCI than in normal subjects (-24% vs. -16%; Fig. 3, middle) (Thompson and others 2013c).

This difference between people with and without SCI in the magnitude of long-term plasticity is reflected in the difference between them in the locomotor effects of H-reflex conditioning. As described above, appropriate H-reflex conditioning markedly improved locomotion in people with SCI (Thompson and others 2013c); while H-reflex conditioning had no detectable effect on locomotion in people without SCI (Makihara and others 2013). The next section considers the etiology of the greater long-term H-reflex change in people with SCI, and its encouraging implications for the therapeutic use of reflex conditioning protocols.

The Impact of H-Reflex Conditioning on Other Behaviors

The spinal cord is a multi-user system; it is the final common pathway for all the behaviors in an individual's repertoire. When a behavior uses the spinal cord, it adjusts spinal reflex pathways to serve its needs. For example, by producing descending influence that modifies presynaptic inhibition at primary afferent terminals on motoneurons, the brain controls the amount of motoneuron excitation produced by the pathway that produces the H-reflex. Figure 6A shows the adjustments associated with a variety of different behaviors, ranging from sitting to standing to walking to running, and in some people, to specific athletic skills, such as playing soccer and ballet dancing (Nielsen and others 1993). These behaviors require different activity levels (or gains) in proprioceptive pathways such as that responsible for the soleus H-reflex. For example, H-reflex gain is decreased from sitting to standing (Kawashima and others 2003) and from standing to walking (Capaday and Stein 1986; Stein and Capaday 1988). Such task-dependent adaptation of reflex pathways is important in ensuring satisfactory production of each behavior.

Each task-dependent adaptation affects only its specific behavior; it does not affect other behaviors. For example, after a person acquires the new behavior of a larger or smaller H-reflex through operant conditioning, task-dependent increase or decrease affects only the H-reflexes elicited in the context of the conditioning protocol. However, over the past several decades it has become clear that the impact of individual behaviors on the spinal cord is not limited to task-dependent adaptations. The acquisition of a new behavior can change the spinal cord itself, it can produce long-term plasticity that affects all the behaviors that use the spinal cord (Thompson and Wolpaw 2014b; Wolpaw 2010; Zehr 2006). That is, it can change the background or default state of the spinal cord on which individual behaviors impose their task-dependent changes. For example, when H-reflex conditioning produces long-term plasticity, it changes the central element in Figure 6A, the baseline strength of the H-reflex pathway. It can thereby affect previously acquired behaviors, which must now use a spinal cord that may not respond to descending commands and sensory inputs in exactly the same way that it did prior to H-reflex conditioning. The functional consequences of this impact on other behaviors differ substantially between people with incomplete SCI and people who are neurologically normal. This difference is likely to account for the fact that long-term plasticity is substantially greater in people with SCI than in neurologically normal people.

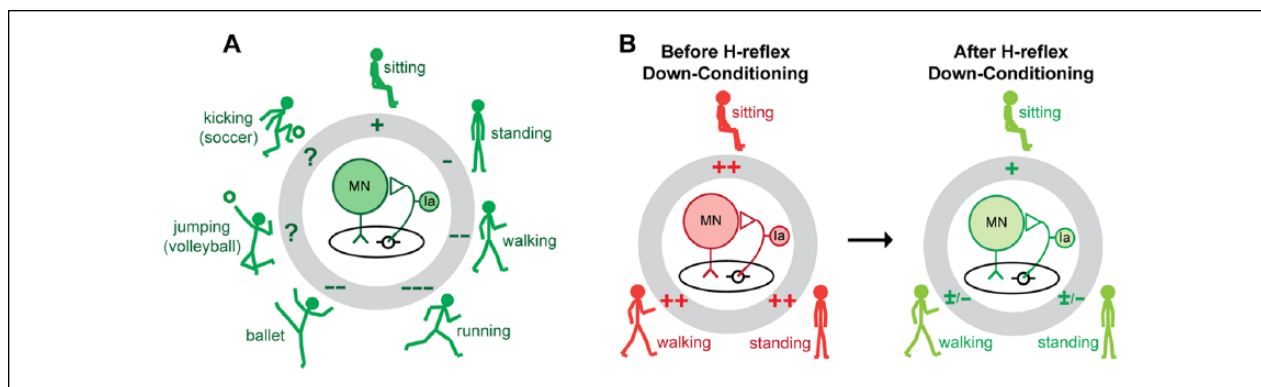


Figure 6. (A) In a neurologically normal person, the spinal reflex pathway (center) responsible for the soleus H-reflex participates in many motor behaviors, ranging from standing to walking to running to athletic skills such as ballet, volleyball, and soccer. Each behavior is accompanied by task-dependent adaptation in the gain of the reflex pathway (pluses or minuses in the gray circle), which ensures that input from muscle spindle afferents contributes appropriately to soleus muscle activation during the behavior (Stein and Capaday 1988). (B) In a person with spasticity due to spinal cord injury (SCI), task-dependent adaptation is impaired, and the pathway is hyperactive during sitting, standing, and walking. Down-conditioning of the soleus H-reflex reduces the gain of the reflex pathway for all three tasks, and thereby improves standing and walking.

In normal people, the long-term plasticity produced by H-reflex conditioning may disturb older behaviors and trigger additional compensatory plasticity that preserves their key features. Indeed, in normal rats, up- or down-conditioning of the soleus H-reflex is associated with other changes that prevent the change in the H-reflex pathway from impairing locomotor symmetry (Chen and others 2011). These compensatory changes appear to be initiated and guided by the brain (Chen and others 2006a; Chen and others 2006c). In contrast, in rats or people with SCI, the long-term plasticity produced by appropriate H-reflex conditioning (up-conditioning in rats with weak stance, down-conditioning in people with spasticity) improves locomotion. Thus, in normal individuals, conditioned change in the H-reflex would ideally consist largely of task-dependent adaptation, with very little long-term plasticity to disturb other behaviors; while in people with SCI, conditioned change in the H-reflex would ideally consist largely of long-term plasticity that improves locomotion. As Figure 6B indicates, this appears to be what occurs. How it occurs may be best understood in terms of the recently proposed *negotiated equilibrium* hypothesis (Wolpaw 2010).

According to this hypothesis, spinal neurons and pathways are continually maintained in a state of “negotiated equilibrium,” a balance that ensures the satisfactory performance of all the behaviors in an individual’s repertoire (Wolpaw 2010). This balance is the result of an ongoing interaction, or negotiation, among the behaviors. Each behavior continually induces plasticity that tends to preserve its key features (e.g., locomotor symmetry) despite the plasticity induced by other behaviors. When the acquisition of a new behavior, such as a larger or smaller

H-reflex, changes the spinal cord, it normally triggers the generation of a new equilibrium that accommodates the new behavior as well as all the old behaviors. Thus, in normal individuals, the long-term spinal cord plasticity produced by H-reflex down-conditioning triggers the negotiation of a new equilibrium that produces a smaller H-reflex and still continues to serve other behaviors satisfactorily. In this negotiation, behaviors such as locomotion that are disturbed by the conditioning-induced long-term plasticity in the H-reflex pathway are likely to oppose this plasticity and limit its magnitude (Thompson and others 2013c). As a result, much of the final change in the conditioned H-reflex consists of task-dependent adaptation, which does not disturb other behaviors.

In contrast, for people with spasticity due to SCI, the long-term spinal cord plasticity produced by H-reflex down-conditioning improves locomotion (Thompson and others 2013c). Similarly, in rats in which SCI has weakened stance, the long-term plasticity produced by H-reflex up-conditioning restores step-cycle symmetry (Y. Chen and others 2006). In both humans and rats with SCI, the long-term plasticity underlying H-reflex change is doubly adaptive: it increases reward probability in the conditioning protocol, and it also improves locomotion. It triggers the creation of a new spinal cord equilibrium superior to the one that prevailed before H-reflex conditioning. Thus, it is probable that long-term H-reflex change is greater in people with SCI than in normal people because it serves more than just a new behavior; it also benefits locomotion. This interpretation is further supported by a recent study that compared the locomotor impact of H-reflex up-conditioning to that of down-conditioning in rats with weak stance due to SCI (Chen and others 2013).

Operant Conditioning as a New Therapeutic Intervention

Investigation of operant conditioning as a new approach to rehabilitation has just begun. In addition to the fact that it is noninvasive and nonpharmacological, the key features of this method are that it is both specific and flexible. By basing reward on the output of a specific CNS pathway (e.g., the soleus H-reflex pathway), it can target plasticity to that pathway; and by selecting the reward contingency, it can strengthen or weaken that pathway as needed. An appropriate operant conditioning protocol could produce targeted plasticity that addresses the specific motor deficits of each person.

Conditioning protocols might target other proprioceptive or cutaneous reflex pathways (e.g., reciprocal inhibition; Chen and others 2006b). Protocols might also target corticospinal connections. The motor-evoked potential to transcranial magnetic stimulation is often reduced after SCI (Barthelemy and others 2010; Davey and others 1999). Initial investigations suggest that the tibialis anterior motor-evoked potential can be up-conditioned in people with SCI, and that this can improve ankle joint movement during locomotion (Manella and others 2013).

It should also be possible to design conditioning protocols that complement existing therapeutic methods, such as partial body weight-supported treadmill training (Barbeau 2003; Edgerton and others 2008; Harkema and others 2012; Wernig and Muller 1992) and constraint-induced movement therapy (Taub and others 1999; Wolf and others 2006), in order to maximize functional recovery. For example, H-reflex down-conditioning might be performed during the swing phase of the step-cycle, when the H-reflex is very small or absent in normal subjects but abnormally large in people with spastic hyperreflexia due to chronic SCI (Stein and others 1993; Yang and others 1991) (e.g., Fig. 1). By targeting the exact time when reflex activity is abnormal, such a protocol might help restore appropriate phase-dependent reflex modulation during walking. Initial results are promising (Thompson and others 2013b). Conditioning protocols are likely to be particularly useful once significant regeneration becomes possible, and new methods are needed to shape the regenerated spinal cord to provide useful function. Finally, conditioning protocols might improve treatment of other peripheral or central neuromuscular disorders (e.g., Chen and others 2010).

While an operant conditioning protocol can target plasticity to a specific pathway, the beneficial impact of appropriate conditioning appears to extend far beyond the effects that can be directly attributed to that plasticity (Fig. 7). In people with SCI, unilateral soleus H-reflex down-conditioning improved the locomotor behaviors of knee and ankle extensor and flexor muscles

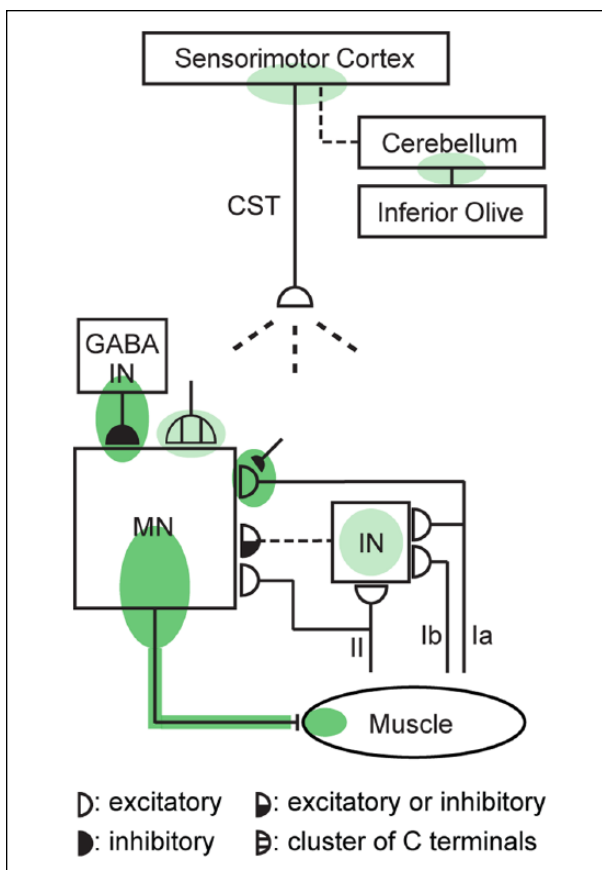


Figure 7. Spinal and supraspinal plasticity underlies H-reflex conditioning. The shaded ovals indicate the sites of plasticity associated with operant conditioning of the H-reflex. “MN” is the motoneuron, “CST” is the main corticospinal tract, “IN” is a spinal interneuron, and “GABA IN” is a GABAergic spinal interneuron. Dashed pathways imply the possibility of intervening spinal interneurons. The monosynaptic and probably oligosynaptic H-reflex pathway from groups Ia, II, and Ib afferents to the motoneuron is shown. Definite (dark green shade) or probable (light green shade) sites of plasticity include: the motoneuron membrane (i.e., firing threshold and axonal conduction velocity); motor unit properties; GABAergic interneurons; GABAergic terminals and C terminals on the motoneuron; the Ia afferent synaptic connection; terminals conveying oligosynaptic groups I and II inhibition or excitation to the motoneuron; sensorimotor cortex; and cerebellum. The latest data suggest that the reward contingency acts through the inferior olive to guide and maintain plasticity in the cerebellum that guides and maintains plasticity in sensorimotor cortex that (via the CST) guides and maintains plasticity in the spinal cord that is directly responsible for the H-reflex change. From Thompson and Wolpaw (2014b).

in both legs, which presumably contributed to the improvement in walking speed and symmetry (Thompson and others 2013c). The plasticity underlying a smaller soleus H-reflex in one leg cannot itself account

for such broad beneficial impact. Together with animal data (Chen and others 2011; Y. Chen and others 2006), this impact implies that H-reflex conditioning triggered additional plasticity in other pathways important for locomotion, and thereby improved the entire behavior. It appears that the acquisition of a down-conditioned soleus H-reflex, by disturbing the post-injury equilibrium that the injured spinal cord had reached, triggered widespread adaptive plasticity that produced a new equilibrium that both decreased the H-reflex and improved locomotion. If comparable processes are triggered by other appropriately selected operant conditioning protocols, the therapeutic value of these protocols may be greatly enhanced.

Conclusions

In people with incomplete SCI, abnormal spinal reflex activity often contributes to chronic motor disabilities. Current therapies are seldom fully effective. Operant conditioning protocols, which can target plasticity to specific reflex pathways, might enhance functional recovery. Indeed, initial studies in animals and humans with incomplete SCI indicate that appropriate operant conditioning of the soleus H-reflex can improve walking. Furthermore, the surprisingly broad beneficial effects imply that a conditioning protocol can trigger widespread plasticity that improves recovery far beyond that attributable to the change in the targeted pathway. Conditioning protocols could be developed to modify other spinal reflexes or corticospinal connections; and might be combined with other rehabilitation methods to enhance recovery in people with SCI or other neurological disorders.

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