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REVIEW

Retraining Reflexes: Clinical Translation of Spinal Reflex Operant Conditioning

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Abstract

Neurological disorders, such as spinal cord injury, stroke, traumatic brain injury, cerebral palsy, and multiple sclerosis cause motor impairments that are a huge burden at the individual, family, and societal levels. Spinal reflex abnormalities contribute to these impairments. Spinal reflex measurements play important roles in characterizing and monitoring neurological disorders and their associated motor impairments, such as spasticity, which affects nearly half of those with neurological disorders. Spinal reflexes can also serve as therapeutic targets themselves. Operant conditioning protocols can target beneficial plasticity to key reflex pathways; they can thereby trigger wider plasticity that improves impaired motor skills, such as locomotion. These protocols may complement standard therapies such as locomotor training and enhance functional recovery. This paper reviews the value of spinal reflexes and the therapeutic promise of spinal reflex operant conditioning protocols; it also considers the complex process of translating this promise into clinical reality.

Key Words Spinal reflex · H-reflex · clinical translation · operant conditioning · plasticity · rehabilitation · neurological disorders.

Introduction

Neurological disorders—including spinal cord injury (SCI), stroke, traumatic brain injury (TBI), cerebral palsy, and multiple sclerosis (MS)—affect many millions of people in the USA and throughout the world (e.g., Table 1). These disorders disrupt the brain's influence on the spinal cord, producing abnormal spinal reflexes that impair motor control. Reflex abnormalities limit mobility (e.g., walking), disrupt sleep, and can cause pain and fatigue [3, 7, 8]. They contribute to spasticity and contractures. Spasticity is one of the most common sequelae of neurological disorders, and a major contributor to functional loss [9–13].

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Currently, the treatment of motor impairments, such as spasticity, includes rehabilitation (physical and occupational therapy [14]) and pharmacological interventions [15–20]. Examples of treatments based on rehabilitation are therapeutic exercise [21], stretching [21, 22], and mobility and gait training [22, 23]. These functional training regimes may include devising new strategies to accommodate motor impairments; and assistive devices may be prescribed to support achievement of patients' functional goals. Pharmacological solutions, such as antispasmodics (e.g., baclofen) and neurotoxins (e.g., botulinum toxin) aim to relieve the symptoms of spasticity by reducing muscle activity [15–20].

However, despite treatment functional mobility and quality of life (QoL) often do not return to pre-injury states or even to functionally useful levels (e.g., a walking speed that enables participation in the community [24–26]). This begs the question: what is the current barrier to effective treatment of spasticity and other motor abnormalities associated with many neurological disorders? The answer, in part, is that current rehabilitation does not target abnormal reflexes.

Reflexes play a crucial role in the control of muscle tone at rest and during movement [27–30]; thus, reflex abnormalities are an important factor in motor impairments [31]. Current understanding of the role of reflexes and the consequences of their abnormalities is based on more than a century of

Table 1 Estimated prevalence and incidence of some neurological disorders in the USA. Note that prevalence and incidence vary across studies [1]

Neurological disorder	Incidence	Prevalence
Stroke	800,000 [2]	7.2 million [2]
Multiple sclerosis	10,000 [3]	350,000 [3]
Traumatic brain injury	1.5 million [4]	3.32 million [3]
Cerebral palsy	10,000 [5]	800,000 [5]
Spinal cord injury	11,000 [6]	285,000 [6]

research, much of which has focused on the H-reflex (or Hoffmann reflex [32, 33]). The H-reflex is a spinally mediated response to nerve stimulation. It is commonly described as the electrical analog of the spinal stretch reflex (e.g., the knee jerk reflex), which is produced by a wholly spinal and largely monosynaptic pathway [28]. H-reflex size indicates the excitability of this reflex pathway. The pathway's excitability reflects the current state of the spinal motoneurons and of the afferent synapses on the motoneurons that are activated by the nerve stimulation [28]. Thus, the H-reflex has long been, and continues to be, a valuable tool for investigating mechanisms of neuromotor control and for elucidating neuromotor impairments [27–30, 34, 35]. For example, in people with SCI, brain control of reflex pathways is impaired [31, 36–38] (i.e., supraspinal connections to the spinal cord are disrupted). This often results in exaggerated stretch reflexes (i.e., hyperreflexia) [31, 36] that impair motor behaviors such as walking. For example, the normal modulation of reflex excitability during walking (e.g., reduced excitability during the swing phase) may disappear, resulting in foot drop, clonus, and other abnormalities [31, 36].

Over the last several decades, the H-reflex has acquired further scientific and clinical importance with the development and exploitation of operant conditioning protocols that can modify spinal reflex pathways. These protocols are among the first of a powerful new class of noninvasive therapies that can target beneficial plasticity (i.e., neuronal and/or synaptic changes that improve important functions such as locomotion) to critical sites in the central nervous system (CNS) (e.g., [39]). Using immediate visual feedback to guide brain activity, they can, for example, change spinal reflex pathways so as to decrease spasticity and restore more normal motor function [37, 40–42]. Spinal reflex operant conditioning has been demonstrated to improve locomotion in studies of animals with incomplete SCI [39, 43] and in several small studies of people with incomplete SCI [41, 44]; other applications are being explored. By targeting beneficial plasticity to an important reflex pathway, operant conditioning protocols trigger wider plasticity that markedly improves important motor functions such as locomotion [39, 41]. Thus, these protocols have the potential to improve the treatment of motor impairments due to neurological disorders; they should be able to complement other therapies and enhance functional recovery.

The therapeutic impact of spinal reflex conditioning on people with neurological disorders hinges on aligning research to support clinical translation [45]. Clinical translation is the process of transitioning from theory, basic science, and mechanistic studies to (in the case of spinal reflex conditioning) a robust, clinically practical, operant conditioning system and protocol. Clinical research oriented toward clinical translation and potentially commercialization is critical to bridging this gap. The key questions for clinical translation reflect many factors, including particularly the market requirements—the needs and wants of those who will buy and use it: rehabilitation clinics, therapists, payors, and the patients themselves. Attention to these factors, coupled with technology development to support clinical research, leads to product development, a business plan, and, ideally, to eventual commercialization and widespread clinical use. This whole process is iterative: clinical research drives further market research and vice versa; and these, in turn, drive further business model and technology development, which can lead to further clinical evaluation.

In this paper, we review current and potential future uses of H-reflex operant conditioning for treatment of motor impairments related to neurological injury or disease. To begin, we first describe the H-reflex in more detail. Specifically, we summarize the procedure for its elicitation, discuss the measurement of the reflex, and summarize insights into nervous system control of muscular function derived from its measurement. This sets the stage for reviewing H-reflex operant conditioning protocols, the steps needed for their successful clinical translation, and the work necessary to accomplish these steps.

The H-Reflex

The H-reflex is a spinally mediated, largely monosynaptic, response to nerve stimulation that was discovered a century ago by Hoffmann [32, 33]. Its size (usually measured by electromyography (EMG)) reflects the excitability of a spinal stretch reflex pathway. The pathway itself consists of group I (and large group II) afferents from muscle spindles (and Golgi tendon organs) that project monosynaptically (and to some extent di- and tri-synaptically) to spinal α-motoneurons, and the motoneurons, which activate the muscle [27–30, 42, 46] (Fig. 1). The H-reflex is elicited in a muscle by electrical stimulation of the nerve that innervates it. In humans, this is achieved noninvasively using surface skin electrodes (i.e., transcutaneous). The size of the H-reflex changes with the parameters of stimulation. As stimulus strength increases, the H-reflex increases to a maximum (Hmax) and then declines as the recruitment of more and more (and

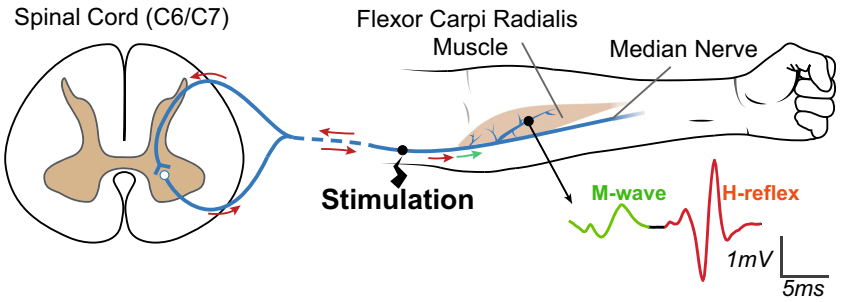

Fig. 1 H-reflex and M-wave pathways for the wrist flexor muscle flexor carpi radialis (FCR). The median nerve is stimulated by a short (0.5-ms) pulse at a current just above M-wave threshold, resulting in two electromyographic (EMG) responses in the FCR. The first is the direct muscle response (M-wave), produced by excitation of a few large α-motoneuron axons (green). The second is the spinally mediated H-reflex, produced by excitation of the largest proprioceptive afferent axons (red)

eventually all) efferent axons into the M-wave prevents them from participating in the H-reflex (i.e., recruitment curves; see [28, 30, 34]).

The H-reflexes of a variety of different muscles have been elicited and studied [28, 30] (Table 2). The ability to elicit the H-reflex is affected by the current level of muscle contraction, the surface accessibility of the nerve, neuromotor pathology, and other factors. For example, an H-reflex can be elicited from the wrist flexor, flexor carpi radialis (FCR), when the muscle is at rest; in contrast, the forearm flexor, brachoradialis, produces an H-reflex only when the muscle is active [28, 30].

H-reflex measures capture the task-dependent nature of reflex pathways [27]. Reflex gain (i.e., H-reflex size at a specific level of ongoing muscle contraction) is lower in standing than in sitting [29, 89–92], lower still during running [89, 93–95]; athletes, such as dancers, show significantly lower H-reflexes during standing but not during sitting [92, 96]. Thus, H-reflex measures help to understand the role reflexes play in movement, and to quantify the effects of reflex abnormalities due to neurological disorders. H-reflex size and latency are recommended (e.g., by Cigna Medical Coverage [97]) for clinical assessments of neuropathies [28, 77, 98] and radiculopathies [28, 61, 99–103]. For example, unilateral radiculopathies can be detected by comparing the H-reflex sizes and latencies on the asymptomatic and symptomatic sides [28, 101–103]. In bilateral radiculopathies, normative values can be used to identify abnormalities [28, 77]. In Fisher's and in Guillain-Barre syndrome, the H-reflex is typically absent [104]. Thus, the H-reflex is part of an ensemble of methods, including the F-wave, imaging (e.g., CT scan), and patient history, that, together, aid in the diagnosis and ongoing assessment of these conditions (see [61] for example).

Decades of research has revealed the value of H-reflex measures to characterize reflex pathways in stroke [27, 82, 105–110], dystonia [111, 112], periodic movement disorders [113, 114], Parkinson's disease [115], and cerebral palsy [116–120]. In people with SCI, for example, changes in H-reflex size and latency evolve from early injury (i.e., the period of spinal shock) to the onset of chronic hyperreflexia [121, 122]. People with spastic hyperreflexia due to SCI exhibit less H-reflex decrease from sitting to standing [93], and the H-reflex is inappropriately elevated during the swing phase of

Table 2 A sample of peripheral nerves, the muscles they innervate, and selected studies of their H-reflexes. (See also [27, 28, 30, 34])

Nerve	Muscle
Tibial (posterior)	Soleus*, gastrocnemius [47–50], flexor digitorum brevis [51], semitendinosus [50, 52], abductor hallucis [53, 54]
Femoral	Quadriceps (vastus lateralis, rectus femoris, vastus medialis) [55–59]
Sciatic	Biceps femoris [50, 60, 61]
Peroneal	Peroneus longus [62–66], tibialis anterior [50, 67]
Median	Abductor pollicis brevis [68–71], flexor carpi radialis [50, 71–79], flexor digitorum superficialis [50, 68, 80]
Ulnar	Abductor digiti minimi [50, 69, 81], flexor carpi ulnaris [50, 81]
Radial	Extensor carpi radialis [71, 82], brachioradialis [50, 83, 84], extensor digitorum communis [67, 81]
Cervical (C3/C4)	Trapezius [85–87]
Musculocutaneous	Biceps brachii [81, 88]

*Many studies have examined the soleus H-reflex ([27] for review)

locomotion [31, 36, 37, 41]. The latter pattern, also observed in stroke, contributes to locomotor impairments such as clonus and foot drop [123].

H-reflex measures have also been used in defining the effects of therapeutic interventions on reflex pathways (e.g., baclofen [124–127], botulinum toxin [128, 129], locomotor training [130–133], cycling [134, 135], muscle stretching [110, 136–139], therapeutic massage [140, 141], whole body vibration [21, 142], spinal cord stimulation [114, 143–146], transcranial direct current stimulation [147] and transcranial magnetic stimulation [27, 148–151]).

One of the features of the H-reflex is that its reliable measurement across sessions can be achieved with attention to key components including the setup (e.g., electrode locations), environment (e.g., temperature), posture/movement of the patient, and time of day [30, 72, 152–155]. For example, muscle and stimulation sites can be kept consistent across days by attending to skin landmarks, such as in the SENIAM project [156]. Grid arrays are promising options for automation of the electrode placement process [157–160]; further work is needed to validate and optimize them.

The H-reflex, however, changes with temperature [161, 162], age [163], caffeine intake [164], muscle circumpressure [165], time of day [155, 166], medication (e.g., [124, 125, 129]), and muscle activation or movement in another limb [27]. For example, hand/arm cycling (i.e., with a cycle ergometer) decreases the soleus H-reflex [167], and ankle plantarflexion (i.e., ankle extension) reduces the FCR H-reflex [168, 169]. Due to these influential variables, care must be used in H-reflex elicitation and interpretation [28, 35]. For example, a stable posture and environment (temperature, comfort) are crucial. In addition, it is important to monitor the background EMG of agonist and antagonist muscles [41]. Joint angle and muscle contraction can also affect nerve stimulation and EMG measurement of the M-wave and H-reflex (e.g., [170]). Thus, it is important to use controls, such as the maximum M-wave, in any study in which limb position is a potential variable or confound. All these considerations are important for any effective effort to translate H-reflex measurement and/or operant conditioning systems and protocols into clinical use.

Evidence that the H-reflex tracks functional outcomes begs the question, why not change the H-reflex directly? Evidence to date supports the hypothesis that appropriate H-reflex operant conditioning can improve function, without adverse side effects. The next sections describe this new therapy, its potential value, and what it will take to translate it into widespread clinical use.

Spinal Reflexes as Therapeutic Targets

Over the past 35 years, many studies have shown that people and animals can gradually increase or decrease the spinal stretch reflex or its electrical analog the H-reflex when they are exposed to an operant conditioning protocol that rewards them when reflex size satisfies a criterion [37, 171–174]. The reflex changes gradually over days and weeks due to plasticity in both the brain and the spinal cord. This plasticity appears to comprise a hierarchy in which the plasticity in the brain induces and maintains the plasticity in the spinal cord [43, 175, 176] (reviewed in [42, 177, 178]).

Figure 2 illustrates the operant conditioning protocol for the human soleus H-reflex [33]. This protocol enables investigators to separate change in the H-reflex due to plasticity in the brain from change due to plasticity in the spinal cord [37]. Furthermore, it enables analysis of the developmental time courses of the brain and spinal plasticity (i.e., neuronal and/or synaptic changes) and of their persistence after conditioning ends [37, 41].

Because the operant conditioning protocol changes the spinal reflex pathway, it affects behaviors, such as locomotion, that use the pathway [179, 180]. This suggested that reflex conditioning could be used therapeutically; the results are very encouraging. In both rats and humans with incomplete SCI, H-reflex conditioning that targets beneficial plasticity (i.e., changes that produce beneficial functional outcomes) to a specific reflex pathway can improve locomotion (Fig. 3) [41, 43, 44]. Furthermore, and most importantly, these initial human studies, and studies in spinal cord-injured rats, indicate that, by producing beneficial plasticity in a key reflex pathway, the operant conditioning protocol triggers wider beneficial plasticity that markedly improves locomotion and persists after conditioning ends. Thus, in humans with incomplete SCI, down-conditioning of the soleus H-reflex in one leg improves locomotor activity in the muscles of both legs; this accounts for the marked improvement in walking speed and symmetry.

Operant conditioning of reflexes is an appealing therapeutic approach to the rehabilitation of locomotion for multiple reasons. First, it is uniquely targeted; it is possible to operantly condition a specific abnormal reflex pathway and strengthen or weaken it as appropriate for an individual person's disability. Second, while continued testing is prudent, there are no known side effects to the conditioning protocol, and it does not affect locomotion in healthy participants [37, 181]. Furthermore, in rats with incomplete spinal cord injury, inappropriate conditioning (i.e., down-conditioning the soleus H-reflex to further weaken stance) did not further impair locomotion [39]. The absence of deleterious effects is likely to reflect appropriate compensatory plasticity; and it is in accord with the negotiated equilibrium model of spinal cord function [177, 178, 182]. Third, in a person with impaired motor function, appropriate reflex conditioning can trigger wider beneficial plasticity [41]. Fourth, evidence suggests that the beneficial effects of conditioning are persistent. In rats with SCI, the beneficial effects of appropriate reflex conditioning continue

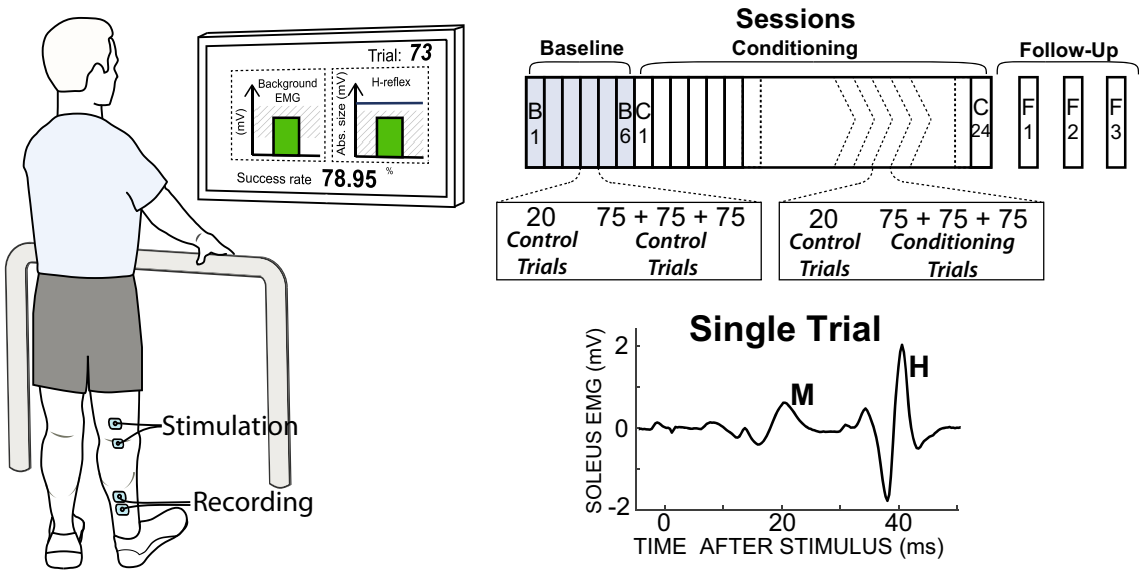

Fig. 2 The spinal reflex operant conditioning protocol. Left—subject with EMG electrodes above the right soleus muscle and nerve stimulation electrodes behind the knee. Subject faces monitor in standard study posture. Monitor displays visual feedback to the subject. In all trials, a background EMG graph shows the correct range and its current value. If the soleus EMG stays in the range for at least 2 s, an H-reflex is elicited. In control trials, there is no feedback as to the size of the H-reflex. In conditioning trials, an H-reflex graph is also shown with a shaded target area. If H-reflex size for the trial falls in the shaded area, the bar is green and the trial is a success; otherwise, the bar is red and the trial is not a success. The screen also shows the success rate for the current 75-trial run. (Modified from [37])

to increase after conditioning ends [183]. And in people with SCI, follow-up sessions showed that decreases in the amplitude of the H-reflex caused by down-conditioning were still apparent three months later [41]. Fifth, reflex conditioning should be able to complement other therapies and enhance recovery. By reducing hyperreflexia, soleus H-reflex down-conditioning can enable more normal locomotion and thereby enhance the effectiveness of locomotor training (e.g., [184]).

Similarly, in people in whom a stroke has produced a disabling flexor synergy in the arm, down-conditioning of a flexor muscle (e.g., FCR) H-reflex might reduce FCR activation by afferent input and thereby enable more effective reach-and-grasp practice. Studies are underway to determine if the effects shown with the lower-limb reflex conditioning protocol translate to the upper limb.

Current research on the therapeutic use of spinal reflex conditioning is focused on extending the results of Thompson et al. [41] to additional populations of people with motor deficits, such as people who have experienced stroke [185] or TBI [186]. Concurrent animal research is exploring its value for improving function after peripheral nerve transection and regeneration (e.g., [187, 188]). Ongoing investigations are exploring the combination of spinal reflex conditioning with other rehabilitation therapies, such as locomotor training [189]. Finally, scientific inquiries continue into the mechanisms of the plasticity in the brain and spinal cord that underlies spinal reflex conditioning (see [42, 177, 178] for review).

Clinical Translation of Spinal Reflex Operant Conditioning

This section addresses what must happen for spinal reflex conditioning to be effectively translated to clinical care of patients with motor impairments associated with reflex abnormalities. Drawing on the material reviewed and the requirements of clinical translation, we identify the scientific, clinical, and translational issues that must be addressed for spinal reflex conditioning to achieve widespread use as a new rehabilitation therapy.

As Fig. 4 indicates, clinical translation proceeds from basic science to clinical research studies to clinical use. In addition to basic and clinical research, it involves market, regulatory, and reimbursement research, and business model and technology development, all informing each other along the way. One of the first steps in the process is identifying and interviewing, as part of market research, key stakeholders to understand their needs and desires [190–192]. For example, clinicians need intervention protocols that are efficient in terms of setup and execution, results that are clinically important in terms of patient function, and a reimbursement model that fits within current policies.

Interviewing stakeholders (users, buyers, and payees) also explores their costs, resources, buying decisions, and regulatory requirements. This initial step in the process of translation helps shape an understanding of the tasks involved in properly positioning the technology for widespread use in the rehabilitation market. These market requirements are used to inform

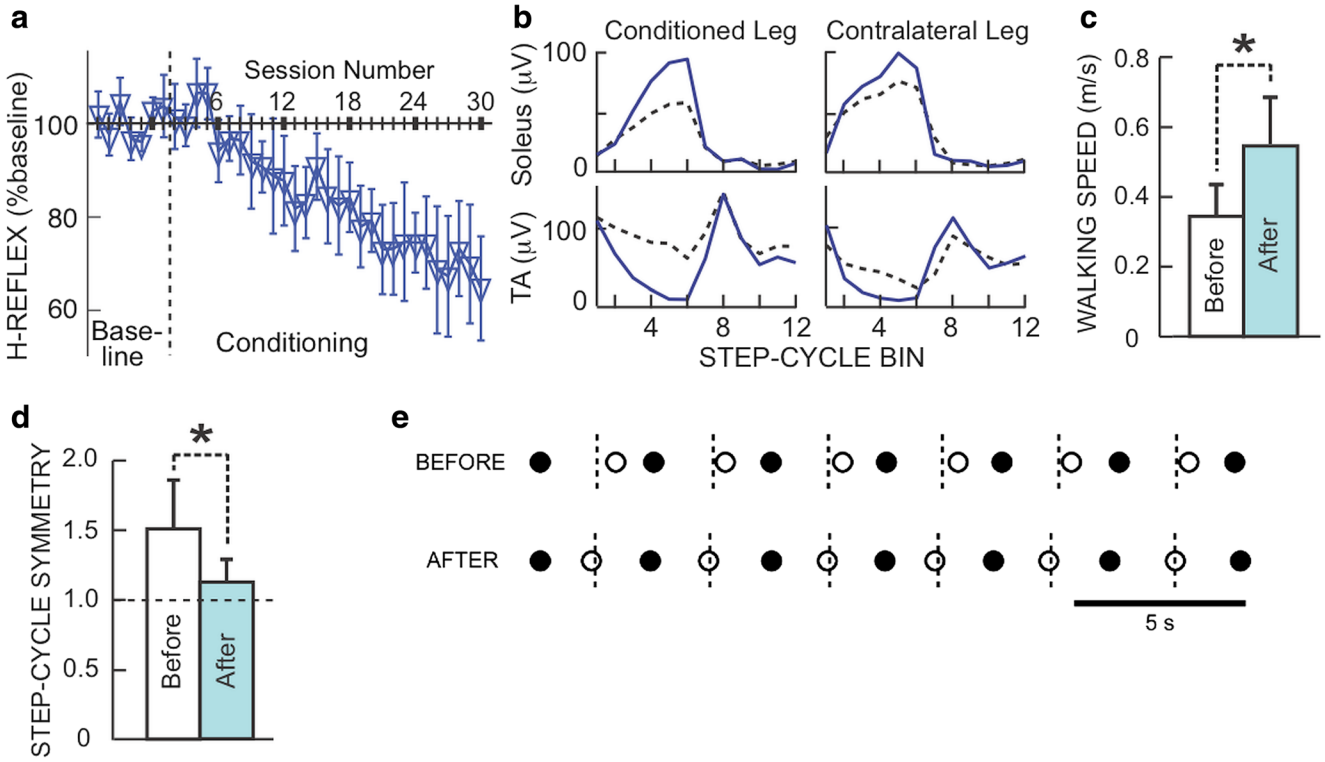

Fig. 3 H-reflex change and walking improvement in people with incomplete SCI who decreased the H-reflex. (**a**) Average (±SE) H-reflexes for baseline and conditioning sessions. (**b**) Rectified locomotor EMG in soleus and tibialis anterior (TA) of both legs before (dashed) and after (solid) H-reflex decrease in a subject. The step cycle is divided into 12 equal bins, starting from foot contact (bins 1–7 are stance, bins 8–12 are swing). After H-reflex decrease, EMG modulation is better in both legs. This helps explain why walking is faster and more symmetrical. (**c**) Average (±SE) 10-m walking speeds before and after H-reflex decrease (*$p < 0.05$, paired t test). (**d**) Average step-cycle symmetry before and after H-reflex decrease (ratio of time between the nonconditioned leg's foot contact (nFC) and the conditioned leg's foot contact (cFC) to time between cFC and nFC). (In each person, the soleus H-reflex of the more impaired leg was down-conditioned.) A ratio of 1 is perfect symmetry. Initially, the ratio is > 1. After conditioning, it has decreased toward 1 in every subject (*$p = 0.05$). (**e**) Successive step cycles in a subject before and after HR decrease. Each nFC (solid) and cFC (open) are shown. Short vertical dashed lines mark the midpoints between nFCs, which is when cFC should occur. Before HR decrease, cFC occurs too late; afterward, it occurs on time. (Adapted from [41])

the product development and overall translation plan. For example, understanding how clinicians weigh the benefits of spinal reflex operant conditioning, with its attendant procedural requirements, against the time demands and the reimbursement challenges [193] is important for designing an effective and feasible clinical system, efficient therapist training, and a viable reimbursement model. How these issues are addressed will help shape the business model for operant conditioning.

In addition, it is necessary to consider the buyer's purchasing threshold. To disseminate spinal reflex conditioning, its cost must be reasonable and justified; i.e., it must provide value to payers, including hospitals and clinics, or to consumers directly, if paid out of pocket. The $30-billion rehabilitation market that spinal reflex conditioning will enter is fragmented; nearly half of the 16,000 rehabilitation clinics are independently owned [194]. Thus, device cost is an important barrier. Extra technological features (e.g., a camera or forceplates to ensure appropriate posture) might introduce insurmountable costs that are a barrier to sales and may not add significant value.

Table 3 provides a broad summary of issues for stakeholders and the role these issues are likely to play in the translation of spinal reflex conditioning. Clearly, the goals differ substantially across stakeholders. Thus, successful

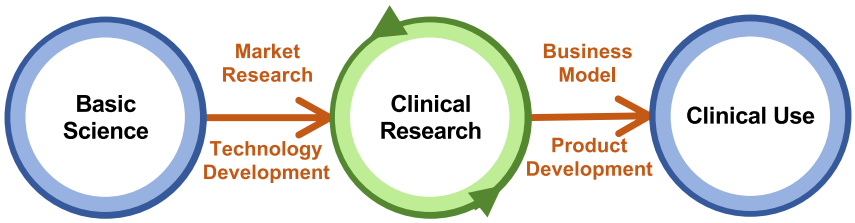

Fig. 4 The process of translation to clinical use following the steps that define the market and the needs of customers/stakeholders within it

Table 3 Key stakeholders in the clinical translation of spinal reflex conditioning. Their roles, goals, and challenges are indicated

Stakeholder	Role in translation	Needs, wants, goals	Challenges
Patients	Participate in operant conditioning treatment; judge effectiveness; pay portion of costs	Improved function (e.g., walking); reduced need for drugs (e.g., baclofen, botulinum toxin); decreased need for assistive devices; improved ability to function in the community	Time commitment; potential cost of device and co-pays
Clinician/therapist	Decide whom will benefit; provide operant conditioning	Clinically important improvement in symptoms and function	Setup and implementation time; deliver outcomes within reimbursement constraints
Clinical administrator	Buy operant conditioning device	High-quality outcomes; marketability and branding/name recognition for state-of-the-art device/therapy	FDA approval; meets clinical need and sustains itself financially; capital investment
Payers	Approve payment for operant conditioning or pay within existing coverage/reimbursement guidelines	Improved outcomes; value; satisfy patient needs	High-quality RCT trials; serve aging population; decrease disability burdens
Researcher	Optimize methods and outcomes of spinal reflex conditioning	Good study outcomes; research papers; knowledge contribution; presentations; patents	Grant funding; tech support; facilities; sufficient time to complete studies

clinical translation of spinal reflex conditioning requires three key items, each forming a part of the overall steps highlighted in Fig. 4:

(i) Strong clinical evidence that a clinically feasible protocol can produce clinically significant functional improvements in key clinical populations (e.g., people with stroke, TBI, SCI, MS, cerebral palsy)
(ii) A cost-effective and implementable reimbursement model
(iii) A robust, easy-to-use, and affordable operant conditioning system for clinical use

Clinical Research Studies

Studies are needed to determine 1) who spinal reflex conditioning will work for and 2) how effectively it works in combination with other therapies. Both are critical in supporting a therapist's decision concerning what therapies to administer.

For example, neurological disorders in which spasticity contributes significantly to functional impairment may be particularly amenable to reflex operant conditioning therapies [38]. On the other hand, people with disorders associated with substantial cognitive impairments may not be able to participate effectively in a reflex conditioning protocol. It is therefore critical to understand in which disorders and/or for which patient populations reflex operant conditioning protocols are most likely to be effective. In addition, conditioning protocols should be developed for an appropriately broad range of muscle groups.

Furthermore, clinical studies need to determine the number and length of sessions necessary to elicit significant functional improvements that persist. For example, the current operant conditioning protocol, which entails 30 1-h sessions, may not be clinically feasible (due to limits on physical therapy visits) and/or might preclude combining reflex conditioning with other therapies (e.g., locomotor training). Thus, clinical research aimed at reducing the number of sessions required is important. Ideally, these studies should establish dose-response curves for different disorders and different motor impairments. In addition, they should enhance the reliability of reflex conditioning (e.g., at present, conditioning is successful in about 70% of people with incomplete SCI [41]).

Clinical studies of spinal reflex conditioning should also evaluate the impact of spinal reflex conditioning in combination with other therapies. The limited evidence to date supports the hypothesis that the combination of spinal reflex conditioning with another effective less targeted therapy, such as locomotor training, will be more effective than either therapy alone [45].

These studies would support clinical uptake and reimbursement by defining the clinical value of the system. It will also be important to address the cost-effectiveness of spinal reflex conditioning and safety [195]. This requires both class-1 (randomized clinical trials (RCT)) and class-2 (e.g., prospective, longitudinal, observational) studies. Class-2 studies often lack the strict controls and randomization of class-1 studies. Real-world class-2 evidence is often more useful and less costly for determining cost-effectiveness, long-term benefits in a variety of patient populations, and other effects of a therapy [195–197]. RCTs are typically conducted in narrowly defined populations, within specialized and very controlled environments by highly trained personnel; thus, they do not reproduce

or relate closely to the complex and continually varying realities of a clinical setting [197]. While class-1 evidence is invaluable for defining relationships between a treatment and its effects, class-2 evidence illuminates a treatment's effectiveness in diverse clinical settings and patient populations, and in the presence of other treatments. Additionally, as medical device development is often incremental, real-world data can provide less costly and a more practical process for continuing to evaluate its safety and effectiveness as its clinical implementation progresses [196].

A Reimbursement Model

A model that defines how a therapy is paid for is a critical step in clinical translation; it is essential for shaping an effective business model for a new therapy. Clinical evidence is critical to determine how clinicians (therapists, physicians, nurses) are reimbursed by insurance companies. Many insurers base their decisions on Centers for Medicare and Medicaid Services (CMS) guidelines [195]. To obtain CMS coverage and payment codes requires substantial supportive class-1 evidence. Payment codes specify the procedures, diagnostic tests, and treatments for which insurance companies and other payers reimburse. However, a payment code alone does not necessarily result in actual payment [195]. In this regard, other evidence (e.g., concerning cost-effectiveness, length of stay, readmission rates, efficacy in a variety of disorders, etc.) is also important and is becoming more so. The clinical evidence needed to ensure actual reimbursement for new medical device treatments is substantial (see [198, 199] for examples of the assessment of functional electrical stimulation devices). The landscape for reimbursement is a large and complicated one. It is therefore important to engage with therapists, insurers, and other stakeholders, including CMS, early on in the clinical translation process.

Technology and Product Development

In its present form, spinal reflex operant conditioning is a complex procedure that uses a cumbersome software/hardware system and requires extensive operator (i.e., therapist) training. Thus, its use is currently limited to laboratory environments and highly skilled personnel. This constraint inhibits its wider clinical use. A robust and easy-to-use system would enable clinical therapists to participate in the further evaluation and eventual dissemination of spinal reflex operant conditioning. This section covers considerations for such a system, including cost and regulations.

To be effective, this clinical system, its accompanying protocol, and associated documentation must ensure appropriate procedures, including maintenance of body and limb posture, appropriate concurrent activation of relevant muscles, electrode placements, stimulation parameters, measurement specifics, and adequate numbers of trials and sessions. In short, standardization and rigorous maintenance of appropriate methods is extremely important. Furthermore, these methods need to be straightforward and convenient so that they can be easily mastered and followed by conscientious therapists. It is essential that the whole process of setup and treatment fit within the work-flow of a busy clinic and conform to the prevailing reimbursement rules for session times and types.

The realization of this practical clinical system is a daunting enterprise. It requires, along with much else, automated algorithms to determine appropriate background EMG activity for agonist and antagonist muscles, detect the M-wave and H-reflex, build M and H recruitment curves, select from them appropriate stimulus intensities, define reward criteria, and update stimulation and reward parameters as needed over the course of treatment. Furthermore, development and validation of each part of the new system entails extensive, highly iterative testing by representative therapists. This guides the development of the product requirements (i.e., what a product should do), including all the technical, usability, and functional requirements of the system.

For example, the selection of recording and stimulation sites seeks to identify electrode locations that 1) are sensitive and specific to the targeted muscle's EMG activity and 2) provide a soleus M-wave/H-reflex recruitment curve that enables stimulation at a level that elicits a small M-wave and an H-reflex on the rising phase of H-reflex recruitment. This site selection task is time-consuming and requires significant training. In a clinically practical system, this onerous task could be avoided by multi-electrode grid arrays [157–160] and an automated procedure that selects the most appropriate electrodes. Figure 5 illustrates the use of such an array for automatic selection of stimulation sites for operant conditioning of the FCR H-reflex. One of the many steps in developing this array is to define the minimum number of candidate electrodes needed to identify the best stimulation sites and to ensure that this identification can be performed within a clinically practical and reimbursable setup time.

Once this initial technological development is complete, it is necessary to finalize product specifications and requirements to initiate a more formal product development cycle. This formal medical device development cycle requires strict adherence to detailed product design and manufacturing principles (e.g., quality assurance). Such adherence and its full documentation are essential for Food and Drug Administration (FDA) approval. FDA classification and regulation is the final step in medical device product development. The FDA defines three classes of devices (Classes I, II, III). Devices are classified according to

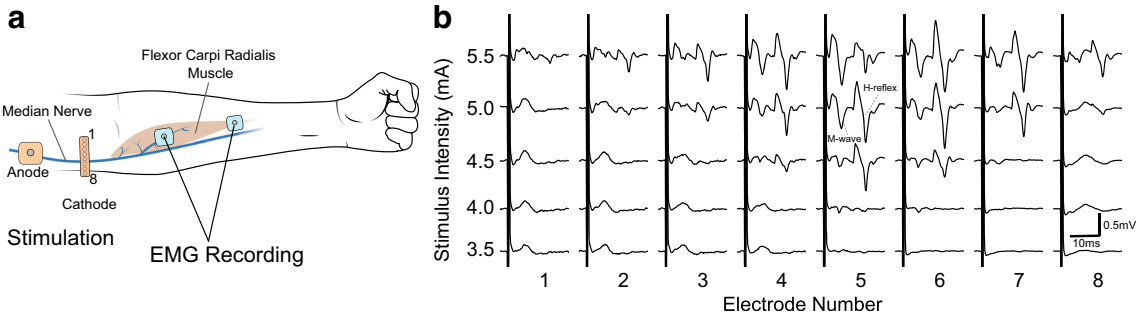

Fig. 5 Automated stimulation-site selection. (**a**) The stimulation cathode electrode is an 8-electrode linear array (1–8; 5 mm between electrodes) (OT Bioelettronica) placed across the cubital fossa to stimulate the median nerve. The anode is placed 2–3 cm proximally, avoiding the biceps muscle (to reduce muscle artifacts). The flexor carpi radialis (FCR) is recorded differentially using two standard 2.2 × 2.2-cm self-adhesive electrodes (Vermed). One recording electrode is placed over the FCR muscle belly, and the other distal to this, on the muscle/tendon junction. An algorithm cycles through each stimulation electrode using a Digitimer DS5 isolated stimulator and a digitally controlled multiplexer (Digitimer D188). (**b**) This produces a series of recruitment curves for each stimulation electrode. The electrode that requires the least current to elicit an H-reflex is identified (i.e., electrode 5)

their risk. For example, a stethoscope is Class I, an ultrasound imager Class II, and an implanted pacemaker Class III.

As a putative Class-II device, a spinal reflex conditioning system has two options for FDA approval. If its intended use and its technical specifications match those of an existing FDA-approved device (i.e., a predicate device), its safety and effectiveness can be determined to be equivalent to those of the predicate device, and it can thereby be approved. If not, it needs to pursue a de novo pathway, a classification path for novel, low to medium risk, medical devices that do not have existing predicate devices. A de novo pathway requires safety and effectiveness data for FDA classification and approval. FDA approval is needed for establishing payment and coverage. The regulation landscape is continually evolving. It is therefore, in general, extremely worthwhile to meet with FDA officials early on to discuss the appropriate regulatory pathway and to ensure that clinical studies and product development are shaped to fulfill FDA requirements.

Conclusions

Spinal reflexes, in particular the H-reflex, are useful biomarkers for evaluating neurological disabilities, for guiding therapeutic interventions, and for assessing the functional effects of these interventions. In addition, the H-reflex is itself a valuable therapeutic target. Noninvasive H-reflex operant conditioning protocols can target beneficial plasticity to critical spinal sites; they can thereby initiate much wider beneficial plasticity that markedly improves important motor functions such as locomotion. These targeted plasticity protocols could complement less specific rehabilitation therapies and enhance functional recovery. The successful translation of this exciting new therapeutic approach into widespread clinical practice requires further clinical studies and hardware/software development, market research, a realistic business model, a viable reimbursement strategy, and regulatory approval. This complex and arduous process has just begun.

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