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Review

Interplay between hypoactivity, muscle properties and motor command: How to escape the vicious deconditioning circle?

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ABSTRACT

Activity-dependent processes addressing the central nervous system (CNS) and musculoskeletal structures are critical for maintaining motor performance. Chronic reduction in activity, whether due to a sedentary lifestyle or extended bed rest, results in impaired performance in motor tasks and thus decreased quality of life. In the first part of this paper, we give a narrative review of the effects of hypoactivity on the neuromuscular system and behavioral outcomes. Motor impairments arise from a combination of factors including altered muscle properties, impaired afferent input, and plastic changes in neural structure and function throughout the nervous system. There is a reciprocal interplay between the CNS and muscle properties, and these sensorimotor loops are essential for controlling posture and movement. As a result, patients under hypoactivity experience a self-perpetuating cycle, in with sedentarity leading to decreased motor activity and thus a progressive worsening of a situation, and finally deconditioning. Various rehabilitation strategies have been studied to slow down or reverse muscle alteration and altered motor performance. In the second part of the paper, we review representative protocols directed toward the muscle, the sensory input and/or the cerebral cortex. Improving an understanding of the loss of motor function under conditions of disuse (such as extended bed rest) as well as identifying means to slow this decline may lead to therapeutic strategies to preserve quality of life for a range of individuals. The most efficient strategies seem multifactorial, using a combination of approaches targeting different levels of the neuromuscular system.

1. Introduction

A chronic reduction in neuromuscular activity, such as during confinement to bed or during aging, is highly prevalent in humans. Acute and prolonged inactivity due to illness or hospitalization affects functional capacity and results in impaired performance in motor tasks, particularly posture and gait [1,2]. In older adults, physical inactivity, although it may be indicated for some patients, always contributes to worsen sarcopenia, whose progression may be greatly accelerated. Inactivity may also aggravate cachexia, in patients with cancer or other chronic diseases. Immobilization in intensive care units may contribute to the survival of critically ill patients but may also lengthen the hospitalization time because of the dramatic decrease in functional neuromuscular capacity [3]. As a consequence, hypoactivity induces a marked increase in the risk of falls and thus predicts several adverse outcomes, including loss of autonomy, decreased quality of life, and even death. In the context of population ageing, age-related diseases and disabilities have become a major health interest, and maintaining autonomy in older people is a challenge. Thus, improving our understanding of loss of motor function under conditions of disuse (such as extended bed rest) as well as identifying means of slowing the decline may lead to strategies to preserve quality of life for a range of individuals.

Mechanisms that cause altered motor performance might be revealed by use of human as well as animal models, to mimic physical inactivity. In humans, the most frequently used models are bed rest [4] and unilateral lower limb suspension (ULLS) [5]. Exposure to microgravity also brings interesting information on neuromuscular plasticity; physiological effects produced by such an environment on the sensorimotor system are close to those of bed rest [4,6]. Some studies have also been conducted in

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subjects with casting of their upper limb [7,8]. This model reproduces immobility but not loss of weight support; therefore, although it can reveal some interesting information, results are often different from those obtained after ULLS or extended bed rest.

In rodents, the model of hindlimb unloading (HU) has been developed to investigate muscle atrophy caused by spaceflight [9]. This model reproduces the loss of charge on both hindlimbs (hypodynamia), reduced limb movements (hypokinesia), and the shift of body fluids toward the upper part of the body. More generally, HU is a valuable model to reproduce bed rest or the effects of inactivity on the hindlimb musculature.

The purpose of this paper is to review recent research into the effects of hypoactivity on the neuromuscular system and to present some rehabilitation strategies that aim to slow down or reverse the altered motor performance.

2. Effect of hypoactivity on the neuromuscular system and behavioral outcomes

2.1. Hypoactivity affects motor behavior

In humans, bed rest leads to degraded postural control, whether after 5 [10], 60 [11] or 90 days [1]. The individuals are unstable on getting up [11], and the incidence of falls increases immediately after bed rest as compared with before [10]. Moreover, performance on a functional mobility test, which consists of completing a course with obstacles as quickly as possible, decreases significantly with bed rest [1]. Arm immobilization by casting alters joint coordination, even for very short duration (12 h) [8], whereas 1 week of joint immobilization affects individuals' ability to accurately maintain a specified contraction level [7]. In rats also, restricted sensorimotor activity affects motor abilities. General motor activity, evaluated by using actimeters, was 50% decreased after a 14-day period of HU [12]. Restricted sensorimotor activity is associated with locomotor impairments such as loss of balance, changes in joint angular amplitude and electromyographic activity, coordination deficits, co-activation of antagonist muscles, shorter strides, and paw dragging [13,14]. The performance on the paw withdrawal test is profoundly altered (i.e., light tactile stimulations elicit less withdrawal in HU rats [15,16]). This test involves not only tactile sensation but also other components such as proprioceptive sensation and motor capacity. Failure of rats under HU to remove the paw might be explained by a postural instability and impaired body support. In humans as in animals [1,10,11,13,17], a total recovery of function is observed within a few days (in general, < 1 week). However, we have shown in rats that despite good locomotor performance, the limb motion remains abnormal, which suggests that the period of recovery corresponds to a new independent plasticity mechanism rather than a simple return to initial characteristics of locomotor pattern [14].

2.2. Hypoactivity affects muscle properties

Several studies suggest that changes in motor performance might be due to muscle weakness [11,18]. Indeed, one of the most important phenomena associated with disuse is skeletal muscle atrophy (decrease in muscle mass and cross-sectional area). Amyotrophy is described after prolonged periods (several weeks) of immobilization by casting or after bed rest [19,20]. However, there are also signs of muscle atrophy after only a few days of disuse (< 10 days) [21,22]. For instance, 5 days of bed rest resulted in an approximately 2% to 3% loss of both the calf and thigh cross-sectional area [23]. Functional atrophy is muscle-specific and more pronounced in postural muscles such as the slow soleus, a plantar flexor. Moreover, the decline in muscle mass is accompanied by phenotypic changes: slow postural muscles become faster. These changes are linked to a decrease in the proportion of slow type fibers and the slow myosin heavy chain isoform [24]. Functionally, a prolonged period of bed rest in humans [25] or unloading in rats [26] results in a decline in muscle absolute and specific forces. Decreased strength is due to cellular and molecular changes in the individual skeletal fibers: loss of myofibrillar proteins, altered excitation–contraction coupling, decreased number of cross-bridges, and lower calcium affinity etc. Finally, from a metabolic standpoint, the activities of glycolytic as well as oxidative enzymes are generally decreased in response to unloading. However, genes related to mitochondrial metabolism are downregulated, whereas levels of those involved in glycolytic metabolism are unchanged. Thus, the metabolic properties are shifted from oxidative to glycolytic metabolism [26].

We have little data on the effect of reloading on the skeletal muscle, and most results are obtained in rodents. In healthy individuals, a complete or partial recovery of morphological parameters (cross-sectional area, fiber length, etc.) seems to occur within the first week, whereas functional parameters (such as peak tetanic force and maximal shortening velocity) do not recover or are even aggravated [27].

2.3. Motor impairments arise from a combination of factors

Some studies have reported that decreased strength is higher than the decrease in muscle mass or cross-sectional area (e.g., [7]), which suggests that the altered motor behavior cannot be caused by muscle factors only. Motor impairments arise from a combination of factors including muscle alteration, impaired afferent input, and plastic changes in neural function throughout the nervous system. Indeed, several authors have shown that after bed rest or ULLS, muscular adaptations coexist with neural adaptations [18,25]. Lundbye-Nielsen and Nielsen [7] even showed that after 1 week of arm immobilization, the altered motor function (decreased maximal voluntary muscle strength and increased variability of the submaximal static contractions) occurred without any change in muscle contractile properties, which suggests that the motor deficit was due to changes in the functional properties of the CNS. A loss of proprioceptive and cutaneous sensations is also an important contributor to the deteriorated postural balance and may increase the likelihood of falling. Although disuse atrophy has received widespread attention and its mechanisms are well elucidated [28], much less is known about the associated alterations in neural properties and brain plasticity.

2.4. Hypoactivity affects the central command

In the nervous system, planning and execution of movements are mainly achieved by the motor cortex. Through corticocortical loops linking sensory and motor cortices, an altered somatosensory pathway in rats under HU might affect the cortical control of muscles. Thus, several studies have evaluated this "use-dependent plasticity" of the sensorimotor cortex. The functional organization of the adult cerebral cortex is characterized by the presence of highly ordered sensory and motor maps. Despite their archetypical organization, the maps maintain the ability to rapidly reorganize in response to a change in sensorimotor experience. In particular, in rats, a whole range of studies performed by our team have provided evidence for a reorganization of the primary somatosensory (S1) and motor (M1) cortices after 14 days of HU: the somatotopic representations of the hindlimb were reduced by $\sim$ 20% in the S1

cortex [15] and ~50% in the M1 cortex [12], and cutaneous receptive fields were enlarged. The S1 somatotopic reorganization was reversed after only a few hours upon a return to a weight-bearing situation [29]. Changes in the excitation/inhibition balance have also been reported. In the M1 cortex, basic electrophysiological features of pyramidal cells were changed, reflecting a short-term decrease in excitability [30]. Additionally, the threshold to evoke a movement was increased, which suggests that corticospinal excitability was decreased [12]. The decrease in cortical excitability, which further amplifies hypoactivity, is characteristic of a hebbian mechanism. In contrast, neuron responsiveness was enhanced in layer IV of the S1 cortex after a low pressure was applied on the foot [31]. The decreased inhibition in the S1 cortex might be explained by neurochemical mechanisms because we [32] and others [33] have described a decrease in GABA inhibition after HU. These changes within the S1 cortex provide a homeostatic response (i.e., a compensatory process that stabilizes neuronal activity despite the decrease in sensory input). These observations suggest that a homeostatic and hebbian use-dependent mechanism occur in conjunction within the sensorimotor cortex [34].

In humans also, arm or finger immobilization by casting has been used to determine whether S1 and M1 cortices are affected by disuse. Data showed deteriorated motor performance and tactile acuity associated with a consistent decrease in S1 cortical activation during tactile stimulation (for review, see [17]). Cortical changes recover 2 to 3 weeks after cast removal [35], but shorter recovery periods have not been explored.

To our knowledge, there are no data on S1 plasticity in response to a bed rest episode. For the M1 cortex, studies are few and results are sometimes conflicting: they depend on the type (bed rest, casting, etc.) and duration of disuse as well as which limb (upper or lower) is affected. After bed rest, a decrease in corticospinal excitability has been reported immediately after a 90-day period of bed rest [36]. In contrast, transcranial magnetic stimulation recruitment curves showed an overall increase in corticospinal excitability after 8 weeks of ankle joint immobilization. However, this modulation of corticospinal transmission is pathway-specific: it concerns only the slow indirect pathway, whereas the direct monosynaptic pathway is unaffected [37]. After a shorter immobilization period (20 days), transcranial magnetic stimulation induced no change in motor evoked potentials in the soleus muscle [38]. Taken together, it appears that hypoactivity procedures, by reducing ongoing cortical inputs and motor cortex output, affect the cortical organization and its structural and functional properties. We assume that, in turn, these alterations in cortical body representation and cortical excitability might participate in the altered motor performance.

3. Hypoactivity leads to a vicious circle

A reciprocal interaction exists between muscle properties and the CNS. Muscles receive a command from motor neurons located within the spinal cord, and in turn, the CNS receives afferent input from proprioceptive and cutaneous receptors (Fig. 1). These sensorimotor loops are essential for controlling posture and

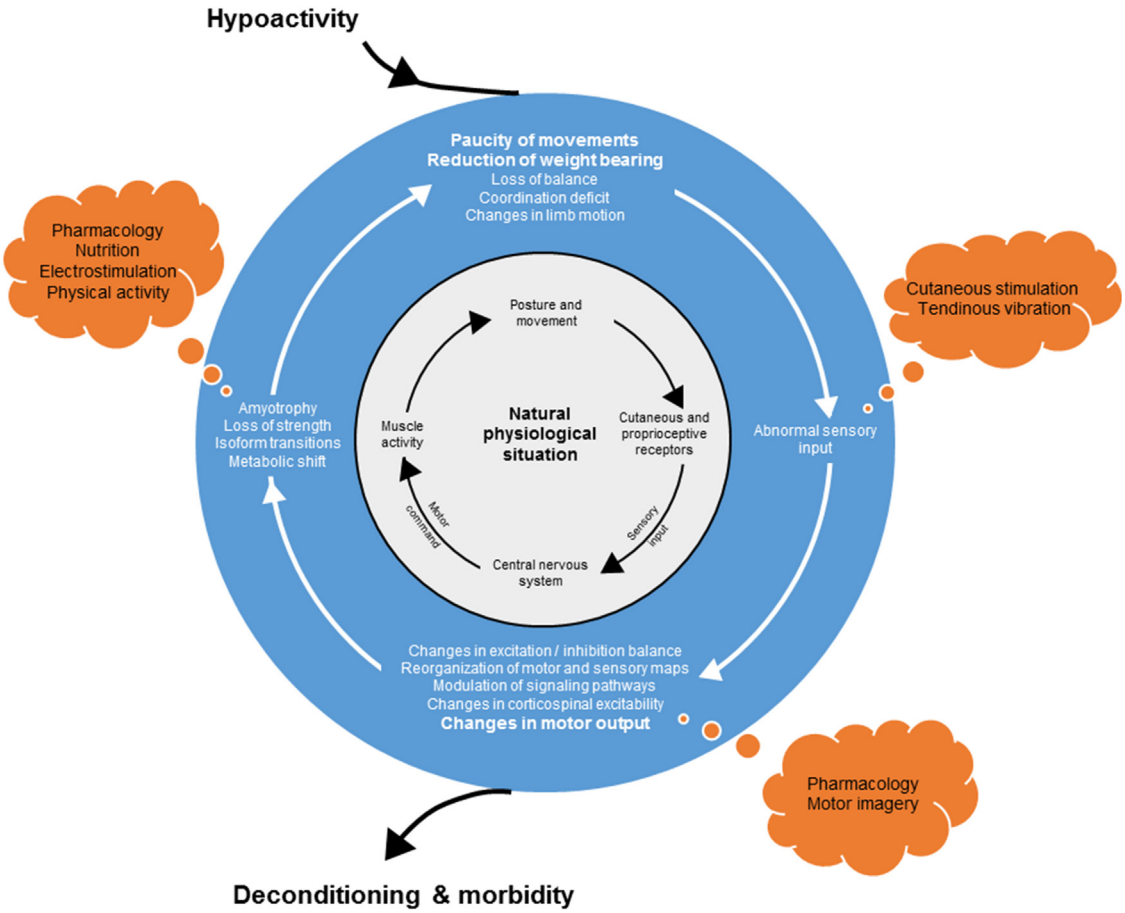

Fig. 1. The vicious circle of deconditioning. Under the normal condition, there is a reciprocal interplay between the central nervous system and the muscle. Movement generates a sensory flow that shapes the central nervous system and thus the motor output. Hypoactivity affects muscle properties, sensory input and neuronal properties, which leads to a progressive worsening of a situation. Some countermeasures to escape the vicious circle are proposed.

movement. In disuse situations, because the force developed by the muscle is reduced and because of the paucity of movements, the resulting proprioceptive input (i.e., reafference) likely changes accordingly. During bed rest in humans, as in animal models of disuse, the proprioceptive and cutaneous input are likely disrupted because:

- the weight-bearing function of the hindlimb extensors is removed;
- movements are rare;
- plantar soles are not in contact with the ground;
- in rats, the ankle is often in a plantar flexion position, and thus the natural physiological stimulus of the soleus muscle spindles (i.e., muscle stretch) is removed [39].

As a consequence, a period of inactivity generates muscle atrophy as well as abnormal sensory inputs, which impair the CNS. This situation generates a decrease in motor command, which in turn affects muscle properties and movement. Reduced and abnormal patterns of movements generate abnormal sensory inputs, and the cycle of inactivity and worsening health continues. In summary, patients under hypoactivity experience a "vicious circle": the cause and effect compound each other and lead to a progressive worsening of a situation. How to escape the vicious circle? Preservation of motor performance, or at least attenuation of deleterious effects of immobilization, supposes that patients confined to bed do not fall into the vicious circle of deconditioning. Various countermeasures have been studied to slow down or reverse muscle dysfunction and the altered motor performance. These protocols were directed toward the muscle, the sensory input and/or the cerebral cortex.

4. How to escape the vicious circle of deconditioning?

4.1. Prevention of muscle wasting

Numerous studies have attempted to learn how to prevent the effects of disuse by exercise. Exercise-based countermeasures are efficient to preserve the integrity and function of the neuromuscular system (e.g., [40]). However, in situations in which strict immobilization is required, this approach cannot be achieved. In these cases, an attempt has been made to restore muscle activity by electrostimulation. When low-frequency stimulations were applied to the soleus muscle in rats under hypoactivity, phenotypic transition but not muscle atrophy was prevented [41]. In humans, the level of evidence for the efficiency of electrostimulation is still low [42].

Pharmacological or nutritional approaches could also be effective. Atrophy is the result of an imbalance between protein synthesis and protein degradation. The predominant signaling pathways contributing to protein homeostasis are now well elucidated [22,43]. Much attention has been given to the ubiquitin-proteasome system and molecules such as myostatin, mechanistic target of rapamycin (mTOR) or the FoxO pathway (for review, see [44]). Protein metabolism can also be modulated via amino acid supplementation. Amino acids are well-known activators of the mTOR signaling pathway. The branched-chain amino acid leucine has received great attention for its role in stimulating protein synthesis [45]. A daily dose (2.7 g/kg body mass per day) of free leucine administered orally, starting 3 days before immobilization, attenuated the loss of soleus muscle mass and strength after 7 days of unilateral hindlimb immobilization in rats [46]. However, whether such a treatment is efficient in humans to reduce muscle wasting is unclear. Of note, in humans, immobilization leads to anabolic resistance [47]: as compared with active individuals, inactive individuals require a higher level of anabolic stimulators to trigger protein synthesis. This anabolic resistance might explain the lack of beneficial effect of nutritional approaches to restore anabolic processes [44]. Antioxidant supplementation is another nutritional intervention that has been found effective in animals. The administration of resveratrol, a natural polyphenol, prevented some deleterious adaptations of muscle properties in rats under HU [48,49].

Although extensive research has been performed to examine the efficacy of therapeutic strategies on muscle mass, the behavioral significance, in terms of motor performance rather than muscle mass or strength, has rarely been examined, and if so, results are often contradictory. In humans under 5 days of bed rest, combined protein ingestion and electrostimulation prevented the decrease in muscle mass but not muscle function [50]. In animals under HU, restoration of muscle force by administration of clenbuterol, an anabolic substance, had no effect on locomotor performance [13].

4.2. Sensory receptor activation

Limb movements in everyday life activate kinesthetic receptors such as neuromuscular spindles but also sensitive receptors located within the skin, tendons, or joint capsules [51]. When people are bedridden, movements are rare, and therefore hypoactivity generates a reduced and abnormal afferent input, which can affect muscle properties. Thus, reactivating accurate sensory inputs might be a way to escape the vicious circle. In humans, although several works have provided evidence of a positive effect of cutaneous stimulation of the lower limb on postural control in healthy individuals, to our knowledge, no study has been conducted in patients confined to bed or under limb immobilization (for review, see [52]).

In animals, intermittent daily vibration of the Achilles tendon (192 s/day) was applied during HU to evaluate whether restoration of sensory receptors input is beneficial for motor function [53]. Tendinous vibration is known to activate mainly muscle spindle primary endings and generate a tonic vibration reflex during which there is an involuntary contraction of the target muscle. This protocol significantly attenuated the soleus atrophy and strength loss induced by unloading but had no counter effect on contraction time or phenotypic parameters. In the same way, application of pressure on the plantar sole for a few minutes per day to activate mechanoreceptors partially prevented some of the muscular modifications (atrophy and strength loss) [54]. These data suggest that tendon vibration and/or plantar sole stimulation can be used as a paradigm to counteract the atrophic process observed after muscle disuse. A preliminary work has been conducted in patients confined to bed after undergoing total knee arthroplasty [55]. The plantar sole and the Achilles tendon were stimulated (80 min/day) for 1 week after surgery. Controls showed alterations in postural control and in the force moment of plantar flexors; these parameters tended to be preserved in the stimulated limb. Of note, in humans with an immobilized arm, besides its potential role on muscle properties, maintenance of proprioceptive inputs via proprioceptive vibration can reduce the effect of limb immobilization on corticospinal excitability of the hemisphere contralateral to the immobilized hand [56].

4.3. Intervention at the cortical level

Clark et al. [18] showed that deficits in central activation of skeletal muscle explain almost half the variability in loss of strength after prolonged unweighting. In addition, some studies have suggested that altered corticospinal excitability should be taken into account to explain the degradation of posture and

locomotion [8,36,37]. Thus, the question is whether cortical manipulation could prevent changes in motor performance.

Continued protein synthesis is necessary to maintain the circuitry supporting motor maps [57]: inhibition of protein synthesis causes a disappearance of the motor map. It also affects skilled limb movement, which suggests that cortical motor maps contribute to motor behavior. After immobilization by casting, the cortex shows a downregulation of genes mainly involved in neuronal signaling and metabolic pathways, which is likely to represent the molecular substrate of use-dependent plasticity [58]. Although the molecular mechanisms of cortical plasticity remain to be clarified, these observations suggest that a pharmacological approach might help prevent detrimental cortical remapping and the associated disturbances in motor behavior. In this perspective, we recently focused on insulin-like growth factor 1 (IGF-1). Present in many tissues, this substance is considered the mediator of the beneficial effects of exercise on the CNS. Indeed, IGF-1 level is increased during exercise and is known to promote cortical plasticity [59]. IGF-1 level is decreased in the sensorimotor cortex of rats submitted to hypoactivity, and activation of its receptor is greatly reduced [60]. We used osmotic minipumps to infuse IGF-1 directly within the cortex during the whole period of rat hypoactivity to restore IGF-1 level. This protocol differentially prevented some of the effects of hypoactivity on the sensorimotor cortex and its deleterious effects on sensorimotor behavior: some cortical parameters totally recovered (i.e., hindlimb representation area within S1), whereas others were only partially prevented (i.e., hindlimb representation area and excitability of M1 cortex, size of receptive fields of S1 neurons) or remained similar to that in rats under HU (i.e., activation threshold of S1 neurons). Functionally, the overall performance on motor and sensory evaluation tests (i.e., spontaneous activity, paw withdrawal after tactile stimulation) totally recovered, although data for the fine kinematic parameters during locomotion were close to those observed in HU rats [12,15].

For many years, mental imagery has been routinely used to optimize performance in athletes. In healthy individuals, it activates structures within the CNS responsible for executing movement, such as motor and pre-motor cortical areas, basal ganglia, cerebellum, etc. This technique is used to increase muscle strength and voluntary activation and thus increase performance in strength tasks [61]. More recently, a therapeutic strategy based on mental imagery has been proposed to preserve muscle performance in patients after injury, immobilization or confinement to bed. Very positive effects were reported after a 4-week wrist immobilization [62]. However, Bassolino et al. [63] did not demonstrate any beneficial impact after a 10-hr period of upper limb immobilization. There are still too few studies on this subject to draw any valid conclusions regarding the efficiency of this therapeutic approach.

5. Conclusion

Hypoactivity alters motor function through muscle impairment and changes in cortical excitability. Degradation in motor function in turn generates a decrease in physical activity, which creates a vicious circle that could lead to deconditioning and increased morbidity. In addition, hypoactivity generates abnormal sensory input that exacerbates the muscular and cortical changes. Hence, the etiology of altered motor output appears complex. The factors involved in deconditioning are multifactorial, encompassing mechanisms such as disuse atrophy and corticospinal excitability.

The present paper is focused on adults. Yet, a sensorimotor restriction soon after birth also leads to degraded motor performance, altered neuronal properties and musculoskeletal pathologies, which persist into adulthood despite cessation of the sensorimotor restriction [64]. A better comprehension of the neuromuscular interplay during hypoactivity in adults might help in developing alternative motor rehabilitation strategies that will also benefit patients who experienced stroke or traumatic brain injury or children with developmental coordination disorders.

Use-dependent plasticity presents 2 opposing components: it might be deleterious or maladaptive (the "Mr. Hyde" effect) because it participates in the degradation of motor abilities in bedridden patients, but it is also a main actor of rehabilitation (its "Dr. Jekyll" nature). The identification of the responses and mechanisms of plasticity might help establish therapeutic strategies. Robot-assisted therapy, with devices such as brain-machine interfaces or exoskeletons, might compensate for the degradation in muscle function by assisting with active movement and enhancing residual function. Restoring movement with such devices might help in generating an appropriate sensory input to modulate corticospinal excitability and thus escape the vicious circle of deconditioning in patients confined to bed. Recently, a combination of muscle vibration and robot-assisted rehabilitation was found to modulate excitability within the CNS and thus improve spasticity after a stroke [65]. In accordance with this study, the most efficient strategies will likely also be multifactorial, with a combination of approaches targeting different levels of the neuromuscular system.

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Disclosure of interest

The authors declare that they have no competing interest.

Appendix A. Supplementary data

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