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TOPICAL REVIEW

Enhancing muscle and brain resilience: The role of prehabilitative exercise in mitigating disuse effects

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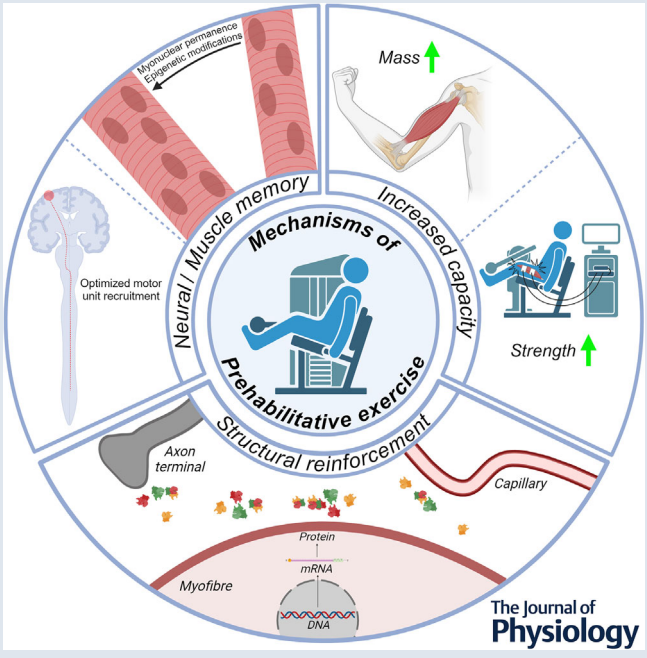

Abstract figure legend Prehabilitative exercise is the process of preparing, through structured exercise, for anticipated disuse (e.g. bed rest or limb immobilization). Despite positive findings in clinical studies, the underlying physiological mechanisms of prehabilitation remain poorly understood. This review discusses three key potential avenues: (1) Prehabilitative exercise may increase the capacity of certain parameters, such as muscle strength, so that losses as a result of disuse less probably force an individual below a critical threshold of function. (2) Muscle memory refers to the retention of adaptations to past stimuli, which can protect the muscle or brain when re-exposed to similar stressors. The location of this 'memory' remains uncertain, but it may involve myonuclear permanence and/or epigenetic modifications in muscle, or changes in neural pathways. (3) Structural reinforcement involves exercise-induced adaptations that strengthen tissues without necessarily increasing their measurable size or function, such as the enhancement of neuromuscular junction integrity and optimization of vascular beds.

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Abstract Short-term disuse leads to rapid declines in muscle mass and strength. These declines are driven by changes at all levels of the neuromuscular system; the brain, spinal cord and skeletal muscle. In addition to neural input from the central and peripheral nervous systems to the muscle, molecular factors originating in the muscle can be transported to the central nervous system. These interactions highlight the interconnected nature of the neuromuscular system during exercise and disuse, and form the basis for this review. Although it is well known that physical activity confers a myriad of health benefits, a recent interest in targeted exercise before periods of disuse or immobility, termed prehabilitation, has emerged. Clinical studies within multiple medical specialities suggest positive effects of prehabilitative exercise on preserving muscle function, reducing adverse outcomes and shortening the length of hospital stay. Yet, the studies available are few and heterogeneous, and the underlying protective mechanisms of prehabilitative exercise remain elusive. In this review, we examine the ramifications of disuse across all levels of the neuromuscular system and explore how prehabilitation may counteract these effects. We summarize these mechanisms into three primary categories: (1) enhancing pre-disuse capacity; (2) establishing neural and muscle memory; and (3) fostering structural adaptations in both muscle and brain.

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Introduction

Skeletal muscle and brain health is essential for maintaining physical function, mobility and overall quality of life. During adult life, and even in old age, new motor (Boraxbekk et al., 2016) and cognitive (Sandberg et al., 2021) skills can be learned, and muscle mass and strength can be improved (Kryger & Andersen, 2007), altogether illustrating the lifelong plasticity of muscle and brain. Initiated in the motor cortex, action potentials are transmitted to motoneurones in the spinal cord, which in turn are transmitted across the neuromuscular junction (NMJ) to the muscle fibre membrane, resulting in force generation through the myosin–actin cross-bridge cycle. Exercise-induced adaptations occur at each place along this path at different rates and at different stages of an exercise training program. For example, initial gains in muscle strength are largely driven by increased neural drive (Del Vecchio et al., 2024), whereas subsequent strength gains rely to a greater extent on addition of cross-bridges through hypertrophy. However, if not maintained by regular exercise, these positive adaptations are lost, hence the term 'use it or lose it'. This is clear in situations with lack of physical activity or outright disuse, where detrimental changes in muscle and brain function are rapidly induced (Mulder et al., 2015; Newbold et al., 2020). Importantly, not all individuals are restored to their pre-disuse levels despite intensive rehabilitation training. Exercise performed prior to a period of disuse, termed prehabilitation, is emerging as a potent strategy to preserve brain and neuromuscular structures and function in healthy and diseased populations, although the mechanisms remain unknown. The goal of this review is to explore the mechanisms by which prehabilitation may preserve neuromuscular function, focusing on the links between central and peripheral neuroplasticity in response to both disuse and exercise.

The dynamic interplay within the neuromuscular system

Skeletal muscle fibres exist as large, multinucleated cells, alongside many mononucleated cell types, which are all

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embedded in an extracellular matrix to form a tissue that is designed to produce and resist forces. As shown in Fig. 1, one of the ways muscle cells communicate with other cells (and organs) is through secretion of factors, and proteomic analyses of the muscle secretome have revealed numerous proteins that are transported through the circulation to other organs where they exert effects (Moon et al., 2019; Roca-Rivada et al., 2012). The most striking evidence of this is in the rodent heterochronic parabiosis and 'runner plasma' experiments, which have wide-ranging effects on multiple cell types and tissues. For example, plasma from running mice infused into sedentary mice reduces experimentally-induced brain inflammation (De Miguel et al., 2021). In addition to soluble factors in plasma, haematopoietic stem cell transplant, such as where the bone marrow of young mice is reconstituted with old haematopoietic stem cells, inhibits hippocampal neurogenesis and impairs cognition (Smith et al., 2020). There is also evidence of factors derived specifically from skeletal muscle, such as vascular endothelial growth factor, promoting neurogenesis in the hippocampus (Rich et al., 2017). Although some studies report increased brain perfusion following exercise (Maass et al., 2015), others find no change in perfusion, despite significant increase in both cognitive performance and cardiorespiratory fitness (Flodin et al., 2017). In clinical populations, interest is emerging in whether preoperative exercise training can positively influence post-operative cognitive function (Ekici et al., 2024), through some of these mechanisms. In general, it appears that blood-borne factors represent a major communication channel between muscle and brain. An alternative path for muscle-neuron communication is through the direct uptake of muscle-secreted factors at the NMJ, which are then transported retrogradely to the motoneurone cell body in the spinal cord (Chakkalakal et al., 2010; Mills et al., 2018; Zahavi et al., 2015). The tetanus neurotoxin uses the NMJ as the point of entry from circulation to the CNS. This toxin binds to the motoneurone pre-synaptic membrane at the NMJ and is transported retrogradely inside the axon to the spinal cord, at a rate of $\sim$7 mm h^{-1}, where it is further transmitted to inhibitory interneurons, resulting in the characteristic

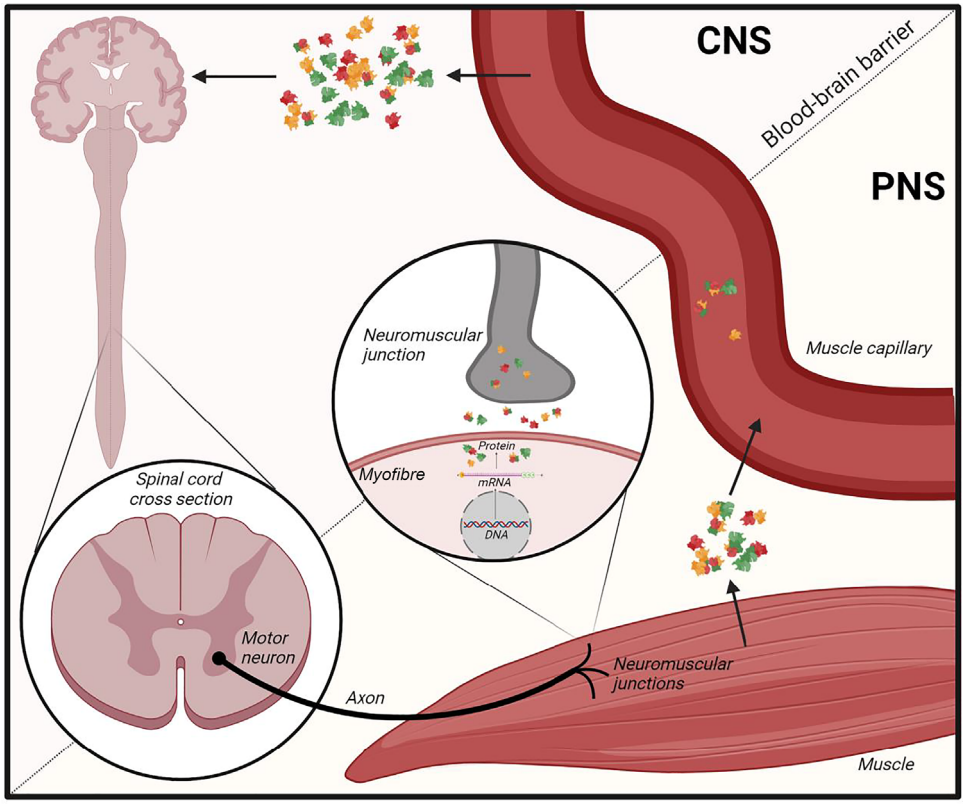

Figure 1. Signalling between the brain, motoneurones, and skeletal muscles
The direct link from the motoneurone to muscle fibre enables bodily movements, through the release of ACh from the motoneurone which initiates an action potential on the sarcolemma. In addition to this antegrade signalling, signalling occurs retrogradely, where muscle-secreted molecules can be taken up at the neuromuscular junction and transported along the motoneurone to the spinal cord. This avenue of access of muscle molecules to the CNS deserves consideration alongside the systemic transport of molecules from muscle to brain. CNS, central nervous system. PNS, peripheral nervous system. Created with BioRender.

tetanic muscle spasms (Schiavo et al., 2000). *In vitro*, uptake of muscle-secreted factors by motoneurones was demonstrated using a microfluidic platform, where the two cell types are cultured in separate (and fluidically isolated) compartments connected by microgrooves through which motor axons can grow and form NMJs with the muscle cells. In this setup, fluorescently labelled muscle-specific glial cell line-derived neurotrophic factor could be seen moving retrogradely along the axons to the motoneurone cell bodies (Zahavi et al., 2015). Furthermore, muscle-to-motoneurone transfer of neurotoxic molecules has been linked to the pathology of amyotrophic lateral sclerosis (Le Gall et al., 2022). It is not known how far these molecules, once in the spinal cord, can travel upstream to the brain itself. However, the alternative access to the CNS via the NMJ, in addition to the more well-studied blood–brain barrier access point, may be valuable to understanding how exercise and disuse impact the CNS. To our knowledge, there is no direct *in vivo* evidence of signalling between muscle and brain through the uptake of factors at the NMJ. Although this may reflect methodological constraints that make it difficult to answer such questions, it may also reflect a less important role for retrograde signalling through the NMJ compared to blood-borne signals. Nonetheless, the neuroprotective effects of exercise appear, at least in the long term, to be largely specific to the active muscles. For example, although master runners have higher numbers of motor units compared to sedentary individuals (Power et al., 2010), this is only observed for the trained leg muscles and not the relatively untrained arm muscles (Power et al., 2012). Importantly, a distinction should be made between the motoneuron, which is the combined functional unit consisting of a motor neuron and the muscle fibres it controls and, in Power et al. (2010, 2012), it is the latter that is estimated. It should further be noted that other studies deploying similar methods have reported no preservation of motor units with lifelong exercise (Piasecki et al., 2016), yet the favourable effects of exercise are conferred through enhanced reinnervation of muscle fibres and improved neuromuscular junction stability (Jones et al., 2022). From the relatively few studies available on this issue, no clear consensus has been reached, but it is interesting that motoneurones exposed to muscle cells from lifelong exercisers appear to be preserved more robustly than when exposed to muscles cells of sedentary peers (Soendenbroe et al., 2024). Ultimately, however, we still do not have a clear picture of the mechanisms explaining the benefits of exercise on muscle and brain structure and function.

Brain and neuromuscular maladaptations to disuse

It is well established that an inactive lifestyle in the long term is associated with chronic disease (Booth et al., 2017). Even short term periods of inactivity (3–7 days), such as during hospitalization, injury or illness, can have a profound negative impact on bodily functions (Bodine, 2013). Many experimental setups have been developed to model the effects of real-life disuse; for example, limb immobilization, bed rest, reduced ambulation, dry-immersion and neuromuscular blockade. In this context, it is notable how bed rest (Di Girolamo et al., 2021; Marusic et al., 2021) or limb immobilization (Campbell et al., 2019; Preobrazenski et al., 2023) consistently cause a decline in muscle strength that exceeds the decline in muscle size. For example, bed rest has been shown to reduce total lean body mass by ∼0.5% per day and knee extension power by ∼1.5% per day (Di Girolamo et al., 2021). Importantly, losses of muscle mass in real-life scenarios might be even larger because these scenarios are confounded by other factors, such as surgical stress and medication usage. For example, a recent meta-analysis showed almost 2% daily losses in muscle mass during intensive care unit (Fazzini et al., 2023). The unequal decreases in mass relative to strength lead to a loss of specific force (force per unit mass of muscle tissue – a measure of muscle quality) (Persad et al., 2024). Tethering the decline in specific force to several points along the path of voluntary muscle contraction has driven many studies in this field. Accordingly, electrophysiology, magnetic resonance imaging and tissue molecular analyses have been instrumental in advancing our understanding of brain and neuromuscular maladaptations to disuse. Below, we examine how the use of these methods has led to an understanding of the time course of these maladaptations.

Although the consequences of limb immobilization perhaps are better understood at the muscular level, there are also studies showing neural adaptations following periods of disuse. For example, glueing the right index and middle fingers together for 24 h shifted the representation in the brain of the ring finger towards the little finger, which was further associated with changes in the ability to differentiate tactile inputs (Kolasinski et al., 2016). In addition, after 2 weeks of arm casting, the regions controlling the disused arm became functionally disconnected from the rest of the somatomotor system (Newbold et al., 2020). Moreover, Garbarini et al. (2019) observed a dynamical shift in the premotor cortex, a brain region with a functional role of action monitoring, with enhanced activity immediately following immobilization. Following 1 week of immobilization, however, the activity was no longer enhanced, suggesting a dynamic shift within this brain region depending on the possibility to execute movements or not. Limb immobilization may also induce rapid neuroanatomical changes including decreased cortical thickness of the immobilized hand area, as well as changes in the white matter integrity (Langer et al., 2012). Whether immobilization has a morphological or a functional origin is not completely known. Some studies have observed no changes in cortical

thickness after 14 days of upper arm immobilization, at the same time as finding changes in the functional connectivity (i.e. a measure of brain region interaction) of brain regions associated with movement planning and error detection (Seo et al., 2024). A functional origin of limb immobilization is further supported by a previous study showing that, although the area of the motor cortex was reduced during immobilization, and correlated with the duration of the immobilization, the reduction was reversed by voluntary muscle contractions (Liepert et al., 1995).

At the muscle tissue level, cessation of muscle activity decreases muscle protein synthesis (MPS) (Rennie et al., 2010). With no appreciable increase in muscle protein breakdown, the decrease in MPS is seen as the main driver of skeletal muscle disuse atrophy (Brook et al., 2022). Rates of atrophy at the whole muscle level are higher during the initial period of disuse (Hardy et al., 2022), and appear to be predominantly driven by atrophy of individual muscle fibres, which has been detected in humans as early as after 3 days of dry-immersion (Demangel et al., 2017) and 4 days of limb immobilization (Suetta et al., 2012). Interestingly, not all muscle fibres, and not all muscles, are affected equally. Indeed, the tibialis anterior appears to be resistant to atrophy, whereas the gastrocnemius is not (Bass et al., 2021), which opens up exciting avenues for mechanistic insights into disuse induced atrophy and how to prevent it. Regarding muscle fibre type, it would seem logical that disuse mostly influences fast-twitch fatigable motor units, and by extension type II muscle fibres, because there is virtually no stimulus to these motor units during bed rest or when wearing a cast. Although atrophy is generally greater in type II *vs*. type I muscle fibres with disuse (Suetta et al., 2013), atrophy is commonly reported for both fibre types (Bamman et al., 1998). Single fibre proteomics has revealed strong downregulation of force transmission pathways, such as cell adhesion and extracellular matrix, with bed rest, and fibre type differences were largely only seen in metabolic proteins (Murgia et al., 2022). Therefore, the effects of disuse reach further than synthesis rates of myofibrillar proteins, and downregulation of force transmission pathway proteins, for example, could potentially partly explain the disproportionate decline in muscle strength *vs*. muscle mass. The differential responses of different muscles, and different fibre types, also need to be considered.

Electrophysiology bridges the peripheral nervous system and CNS to get closer to the motor unit level although it remains unclear whether type I or type II motor units are more susceptible to disuse. For example, motor unit potential properties, as determined by I.M. EMG recording, are altered in response to single leg immobilization in young healthy men (Inns et al., 2022; Sarto et al., 2022). These recordings are based on low intensity contractions (10% and 25% of maximal voluntary contraction force), which predominately assesses slow-twitch fatigue-resistant (type I) motor units, thus reflecting a response in type I motor units and highlighting a lack of robust data on type II motor units. Regarding the source of the altered motor unit properties recorded with disuse, intriguingly, NMJ transmission stability remained unaltered (Inns et al., 2022; Sarto et al., 2022), suggesting that, at least for type I motor units, the negative effects of prior disuse are not detectable at the NMJ itself but probably occur elsewhere in the motoneurone. By contrast, molecular studies suggest perturbations to NMJ structure and function with prolonged periods of inactivity (Bodine, 2013). Unloading hindlimbs or blocking neuromuscular transmission in rats causes morphological alterations at both the pre- and post-synaptic compartments of the NMJ (Deschenes & Wilson, 2003; Lee et al., 2023), whereas tissue gene and protein markers of innervation stability are upregulated with disuse in humans (Arentson-Lantz et al., 2016; Demangel et al., 2017; Monti et al., 2021; Pillon et al., 2020; Sarto et al., 2022). The discrepancy between EMG and tissue analyses might be based on the type of motor units being assessed. In the context of specific force, it is interesting to note that impaired motor unit properties are fully restored after 21 days of resistance training based recovery in young men (Valli et al., 2024), suggesting that persistent deficits in specific force are due to failed recovery at other sites of the neuromuscular system.

Brain and neuromuscular adaptations to exercise

Because of the rapid loss of muscle function with disuse in clinical conditions, it is important to determine which type of muscle stimulus provides the strongest boost to muscle function before, during and after disuse. Numerous interventions during disuse appear promising, such as resistance exercise, endurance exercise, physiotherapy or electrical stimulation (Ferrando et al., 1997; Hansen et al., 2024; Hasegawa et al., 2011; Karlsen, Cullum et al., 2020; Kawakami et al., 2001; Reidy et al., 2017; Zinglersen et al., 2018). In a 12 week bed rest study in healthy young men, heavy resistance exercise of the lower limbs every third day, in bed, completely ameliorated the decline in muscle strength (Trappe et al., 2004). However, for some individuals or hospitals, this type of training may not be feasible during hospitalization. As an alternative, electrical stimulation of the quadriceps muscles three times daily preserved thigh muscle mass during 5 days of bed rest in younger and older men and women (Hansen et al., 2024). However, this stimulus was not sufficient to preserve muscle strength, highlighting the importance of central activation of muscle for function.

Studies across several months have suggested a possible relationship between being physically active and brain

structure and function. For example, cardiovascular exercise can improve cognitive functions (Jonasson et al., 2016), and increase (Erickson et al., 2011) or maintain (Demnitz et al., 2022) the size of the hippocampus, an important brain region for consolidation of new memories. Furthermore, functional connectivity during rest may be related to changes in cardiorespiratory fitness, primarily within the medial temporal lobe, which contains several anatomically related structures involved in learning and retaining information (Flodin et al., 2017; Voss et al., 2011). Given that changes in hippocampal volume and perfusion are associated with changes in cardiorespiratory fitness, the benefits of exercise appear to be mechanistically linked to a strong coupling between neural and vascular plasticity (Maass et al., 2016). It should be noted, however, that the field in general is showing considerable individual variability in the link between physical exercise and brain health, with several studies not showing the proposed relationship. A recent strength training intervention, for example, observed no brain grey matter volumetric changes (unpublished data), despite a considerable improvement, and long-term maintenance of leg strength (Bloch-Ibenfeldt et al., 2024; Gylling et al., 2020). There have also been several meta-analyses questioning the capacity of physical exercise to improve cognitive performance (an umbrella review of randomized controlled trials of the effects of physical exercise on cognition is provided by Ciria et al., 2023) and understanding individual variability in the response is the necessary next step to understand the potential, if any, of exercise to strengthen brain structure and function. From a mechanistic point of view, in addition to interventions lasting several months, studies investigating the effects of a single bout of exercise have been used. Here, a single bout of exercise has, for example, been shown to induce rapid enhancement in the cognitive function of pattern separation, such as our ability to dissociate different memories so that they are stored (and retrieved) separately from each other, accompanied by increased functional coupling between hippocampal and cortical regions (Suwabe et al., 2018). Furthermore, a single session of aerobic exercise mimics the effects of 12 weeks of exercise on performance of a working memory task, including effects on functional connectivity (Voss et al., 2020). Thus, the initial physiological brain effects may act as an activity-evoked biomarker for the continued neuroplastic long-term effects (Voss et al., 2020). Further investigations are needed to understand the exact mechanisms, although it is probably also related to immediate changes in brain metabolism (Ryberg et al., 2023). How long these adaptations last, however, and whether they can offset changes induced during disuse, remains unknown. Notably, 60 days of bed rest using a 6° head-down tilt paradigm induced increased activity in the hippocampus during a memory encoding and retrieval task (Friedl-Werner et al., 2020). This accelerated pattern of ageing was reversed with physical activity, also in the supine position, during the study period. Thus, the proposed functional changes that may lead to an increased demand for neurocognitive control following bed rest (Yuan et al., 2016), may be reversible with physical activity, but future studies are needed to address this further.

Similarly, for muscle, studies tend to focus on several months of exercise training or a single bout of exercise (Lavin et al., 2019). Focussing on innervation specifically, a single bout of heavy resistance exercise influences the gene expression of the ACh receptors in a subunit specific and temporal manner (Soendenbroe et al., 2020), demonstrating that muscle innervation is dynamically regulated. When this exercise was performed for 8 weeks, it led to significant reductions in markers of muscle denervation, concomitant with increases in muscle strength (Soendenbroe et al., 2022). These findings support studies in rodents, showing that exercise improves NMJ morphology (Cheng et al., 2013; Valdez et al., 2010) and transmission efficiency (Chugh et al., 2021).

The rapidness of these exercise-induced effects in both brain and muscle suggests a possible beneficial role for exercise conducted prior to disuse (i.e. prehabilitative exercise). From a societal perspective prehabilitative initiatives might shorten length of stay, reduce the number and severity of post-surgical complications, and lead to overall improvements in patient quality of life. Prehabilitative exercise has the embedded benefit that it can be performed away from the hospital and closer to the patient's home, such that the patient is not affected by surgical stress and can be more actively involved in their own treatment. Accordingly, several meta-analyses have shown mostly positive effects of prehabilitative exercise on clinical outcomes and *in vivo* measurements of physical function (Bruns et al., 2016; Cabilan et al., 2015; Duro-Ocana et al., 2023; Heger et al., 2020; Jørgensen et al., 2022; Marmelo et al., 2018; Perry et al., 2021; Piraux et al., 2018). However, because prehabilitation has been markedly less studied than rehabilitation, the meta-analyses suffer from a low number of studies, heterogenous interventions (type of exercise, number of sessions, duration) and generally a low quality of evidence. This complicates the interpretation of what an effective intervention prior to disuse for specific populations entails. Furthermore, prehabilitative exercise, similar to all exercise interventions, is subject to inter-individual variation in response (Ross et al., 2019). It is therefore important to consider how many individuals will benefit from a given intervention, how long the intervention should last and how frequently exercise should be prescribed.

From an exercise physiology perspective, significant improvements in cardiorespiratory function occur after as little as 2 weeks of high-intensity interval training (HIIT)

in young and older adults (Herrod et al., 2020). Similarly, 4 weeks of home-based, non-supervised, resistance exercise improved muscle strength in older adults (Cegielski et al., 2017). These significant improvements in a matter of weeks demonstrate that, although the time from medical decision to surgery might be short, this window is not too small to deliver effective exercise training. In terms of mechanisms explaining the benefit of prehabilitation, muscle damaging exercise or resistance exercise conducted before bed rest or immobilization has revealed mixed outcomes. Although muscle damaging exercise partially prevented declines in muscle volume and MPS at 2 and 7 days of immobilization, muscle strength was negatively impacted, questioning the suitability of damaging exercise in patient populations (Jameson et al., 2021). Four bouts, or a single bout, of resistance exercise prevented the declines in MPS with bed rest, with mixed outcomes for muscle size, although we lack strength data to fully evaluate the merit of such prehabilitation approaches (Smeuninx et al., 2021, 2023). In animal studies, treadmill running interventions of varying duration (one session to 8 weeks) generally preserves muscle mass (Fujino et al., 2009; Nakamura et al., 2017; Theilen et al., 2018) and specific force (Yeo & Lim, 2023) during subsequent hindlimb unloading, although this effect is not consistent (Yee et al., 2023). Taken together, insight into the mechanistic underpinnings of prehabilitative exercise is very limited and somewhat confounded by the influence of tissue damage. Given the promising results of prehabilitative exercise on clinical outcomes, there is a need to investigate these mechanisms further, from an integrated muscle–brain perspective. It is equally important to conduct these mechanistic studies in patient populations because the response to exercise might be influenced by the disease burden itself, as observed with the inability to increase MPS with HIIT in urological cancer patients pre-surgery (Blackwell et al., 2023).

Potential mechanisms underpinning protective effects of prehabilitation

Given the complexity of neural and muscle interaction, it is perhaps not surprising that the mechanisms underpinning the protective effects of prehabilitation are not immediately apparent. The main potential mechanisms considered in this review are increasing pre-disuse capacity, structural reinforcement and neural/muscle memory.

As illustrated in Fig. 2, there is a change (usually a decline) in any given parameter with disuse. This is restored by a return to normal activity levels or some form of rehabilitation, such as resistance training. With prehabilitation, the baseline before disuse can be moved, for example, by increasing muscle mass and strength, or in other words, increasing the pre-disuse capacity. The data reviewed here do not show complete protection against declines in these parameters, but rather an amelioration. However, the picture is incomplete as a result of too few studies including prehabilitation. Several outcomes are possible. For example, having a higher pre-disuse level might lead to even greater loss of muscle mass. Younger individuals appear to lose more muscle mass than older individuals (Suetta et al., 2013), although it is not clear whether this simply reflects a slower adaptation of older muscle to any condition. It is also unclear how sarcomeric proteins are turned over during a dynamic situation such as prehabilitation where newly synthesized proteins are being added. Muscle fibres increase in size radially through addition of myofibrils rather than expansion of existing myofibrils (Jorgenson et al., 2024). However, protein degradation appears to be independent of protein age, indicating that older proteins and newly synthesized proteins are equally susceptible to degradation (Douvdevany et al., 2024), although how this is impacted in a dynamic situation such as atrophy immediately after hypertrophy is unknown, as discussed extensively elsewhere (Sayed et al., 2023). Regardless of the mechanism, it appears that prehabilitation does not pre-

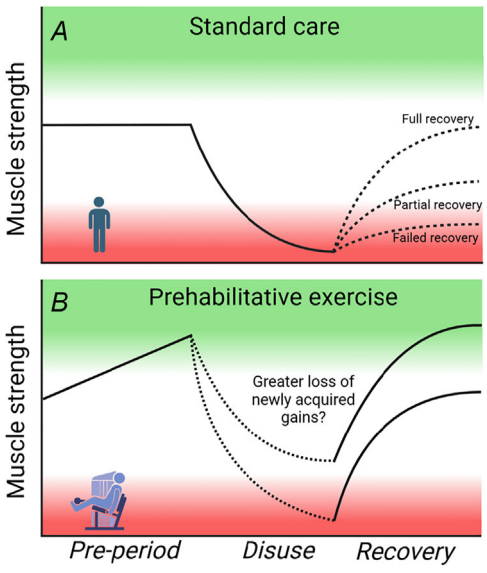

Figure 2. Mechanisms of prehabilitation exercise in protecting the neuromuscular system during disuse
A, in the absence of prehabilitation, declines are seen in most parameters. Recovery is usually complete but not in all individuals, especially older persons. *B*, prehabilitation can boost levels of muscle and brain structure and function, for example muscle strength (as shown), synapse integrity and vascularization. Such adaptations may not protect against declines during disuse but could promote a more complete and rapid recovery. Alternatively, the higher level achieved during prehabilitation might be maintained during disuse. The outcomes are probably dependent on the parameter in question.

vent against disuse-induced muscle atrophy or strength. Rather, it is more probable that the pre-disuse training allows for a more complete, or even faster, recovery afterwards.

One of the most probable mechanisms underpinning this response is muscle memory (Gundersen, 2016), the phenomenon of returning to a specific exercise, for example resistance training, and progressing in strength much faster than when initially taking up the exercise, even with years of a break. The big question is where this memory resides. There is evidence to support 'neural memory', as well as 'local memory' (in the muscle fibres themselves). Neural memory relates to acquiring the skills to perform a specific motor task and is commonly used to explain the phenomenon of never forgetting how to ride a bike, even after many years (Monfils et al., 2005). In the context of prehabilitation, training the leg press as a mode of prehabilitative resistance exercise creates a motor representation in the brain, whereby patterns of motor unit recruitment are established, along with adaptations at the muscle tissue level, such as hypertrophy and strengthening of the muscle–tendon unit to withstand and transfer force. Then, after a period of disuse, the motor representation is already in place, so the skill learning phase can be skipped, accelerating the strength gains achieved once the exercise is resumed. The important questions are (1) how much prehabilitative exercise is needed to create a sufficient degree of motor representation and (2) how long does it last? Local tissue memory has been suggested as an alternative mechanism, explained by myonuclear permanence (Cumming et al., 2024), and epigenetic modifications at the cellular level (Sharples & Turner, 2023). Both local muscle tissue memory and neural memory probably contribute to this phenomenon. For example, using lineage tracing in mice, Murach et al. (2022) showed that myonuclei derived from satellite cells during 8 weeks of progressive weighted wheel running were epigenetically specialized for regulation of transcription factors. Furthermore, satellite cells in culture retain traits of donor age and exercise status (Bechshøft et al., 2019; Green et al., 2013), and it can be speculated that disuse imprints on the cells, altering the cellular profiles. For example, treatment with Metformin, a drug known to possess senolytic effects, from 2 weeks before and during a 5 day bed rest period, reduced expression of senescence markers *in vitro* (Petrocelli et al., 2023). In other situations, there is evidence for priming a muscle with exercise to enhance repair after subsequent muscle injury (Joanisse et al., 2016). This approach has also been tried in reverse, by priming the muscle by injury to enhance the exercise response. In this study conducted in older humans, it was hypothesized that forcefully activating the satellite cells through electrically induced eccentric contractions would precondition a muscle for resistance exercise, leading to greater hypertrophy (Karlsen, Soendenbroe et al., 2020). However, no effect was seen, potentially because of an equally robust hypertrophy response in the uninjured leg as the injured leg (Karlsen, Soendenbroe et al., 2020). The advantage of exercise preconditioning had been suggested to be linked to expansion of the muscle stem cell pool and vascular network. Indeed, structural changes such as vascularization may reinforce brain tissue for subsequent periods of physical disuse. Similarly, the reinforcement, or fine-tuning maintenance, of synapses is a potential protective mechanism relevant for both brain and muscle. Whether the more robust NMJs as a result of rehabilitation could offset the NMJ instability reported with disuse remains to be seen.

Conclusions and future directions

Disuse and physical inactivity lead to sharp decreases in physical function, as a result of adaptations in the neuromuscular system, from the brain, through the spinal cord to the neuromuscular junction and the muscle fibres themselves. Molecular and electrical communication occurs between the different cell types of the neuromuscular system, necessitating multiperspective approaches to study the mechanisms of disuse-induced muscle weakness. In some cases, disuse can push an individual below the threshold for independent living, highlighting the need to identify effective treatment regimens that may ameliorate the debilitating effects of disuse. In this context, prehabilitative exercise appears promising from clinical studies, yet the underlying mechanisms remain undefined. Indeed, studying muscle–brain adaptations in an integrated manner may help identify mechanisms behind the benefits of exercise and detriments of disuse, which would pave the way for preserving physical and cognitive function.

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Additional information

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The authors declare that they have no competing interests.

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