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EDITORIAL

The dynamics of neuromuscular resilience across the lifespan: Ageing, disuse and intervention

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The integrity of the neuromuscular system (NMS) is a critical determinant of human mobility, health and safety over the life span. Its function, however, is continuously contested by a confluence of biological stressors: primarily intrinsic progressive biological ageing, acute periods of disuse and the molecular perturbations induced by chronic disease. This special issue of *The Journal of Physiology* is dedicated to dissecting these challenges, offering a collection of innovative original research, translational reports and essential technical advancements that collectively advance our understanding of the NMS from the supraspinal cortex to the molecular dynamics of the myocyte.

This compilation is structured around three core pillars: *Vulnerability*, which explores the fundamental biological mechanisms of pathological decline; *Acute Stress*, which investigates the rapid and maladaptive changes induced by physical inactivity; and *Resilience*, which assesses the efficacy and mechanistic underpinnings of targeted physiological interventions. Collectively, these articles illuminate the remarkable, yet diminishing, plasticity inherent in the motor system, and critically, how this plasticity may be harnessed to safeguard functional capacity throughout life.

Vulnerability: unravelling the intrinsic mechanisms of decline and pathology

The articles herein move beyond merely documenting functional decline to meticulously unravelling the multiscale, mechanistic drivers of age-related degradation and pathology. The challenge is framed not as a solitary muscular or neural failure, but as a system-wide breakdown.

The emerging concept of the bone-muscle-nerve triad is explored in the context of osteosarcopenia (Karacan & Türker, 2024). This research delves into the neuronal interactive communication underlying the common co-existence of osteoporosis and sarcopenia, termed osteosarcopenia. While mechanical and humoral coupling mechanisms are well-established, this review focuses on the less-explored nervous system involvement. Karacan & Türker (2024) describe the bone myoregulation reflex, a proposed spinal segmental mechanism where the mechanosensitive osteocytic network acts as a receptor, transducing mechanical load into neural signals transmitted to the spinal cord. This information then reflexively regulates skeletal muscle function via alpha motor efferent fibres. Karacan & Türker (2024) argue that age-related regressive changes in osteocyte function and proprioceptors probably disrupt this neuronal communication, contributing significantly to the pathogenesis of senile osteosarcopenia.

With an emphasis on the cortico-spinal level, Taube and Lauber (2024) analyse the cortical GABA inhibitory system, detailing its pivotal role in motor control and cognition. As the primary central nervous system inhibitory neurotransmitter, GABA regulates cortical excitability via fast and slow inhibitory mechanisms (such as short-interval and long-interval intracortical inhibition). Healthy ageing is associated with reduced global GABA levels and impaired inhibitory control, correlating with declines in motor and cognitive function with reference to postural control. This imbalance is exacerbated in neurodegenerative diseases such as mild cognitive impairment, showing deficits in both GABA concentration (measured by magnetic resonance spectroscopy) and function (assessed via transcranial magnetic stimulation techniques). The review is noteworthy to present evidence that targeted physical activity, specifically challenging coordinative balance tasks acts as a countermeasure, upregulating sensorimotor GABA concentrations and enhancing task-specific inhibitory modulation in older adults, thereby challenging the long-held view of the aging brains fixed capacity for plasticity.

Furthermore, the issue provides a timely reminder of the necessity of considering sexual dimorphism in neuromuscular ageing. The paper on female neuromuscular function across the adult lifespan by O'Bryan et al. (2025) maps a non-linear decline in quadriceps voluntary and evoked torques, with accelerated reductions beginning during the fourth decade of life, coincident with menopausal onset. The study found no significant age-related changes in central measures such as voluntary activation or H-reflex amplitude, suggesting the functional decline is predominantly mediated by intrinsic peripheral muscle function and/or neuromuscular transmission impairment. This peripheral vulnerability is supported by the specific age-related decrease in the rectus femoris maximal compound action potential amplitude. Critically, in postmenopausal females, the decline in torques was significantly correlated with inter-individual differences in quadriceps tissue composition, lifestyle factors and changes in total or free concentrations of oestradiol, progesterone and/or testosterone.

Beyond primary ageing, chronic pathologies impose distinct burdens. Lecce et al. (2025) investigate the physiological mechanisms of neuromuscular impairment in diabetes complications, positioning the condition as a model of accelerated ageing. The review details widespread deterioration

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stemming from neurogenic (neuropathy) and non-neurogenic (myopathy) factors, including structural damage to the motor cortex and spinal cord, demyelination, and accelerated loss of motor axons and muscle fibres. The underlying pathology involves persistent hyperglycaemia-induced oxidative stress, advanced glycation end-products and compromised vascular supply, all contributing to dysfunctional motor unit firing patterns and significant declines in muscle strength, power and endurance. Crucially, Lecce et al. (2025) assess the potential for physical exercise to counteract these declines by promoting muscle strength and hypertrophy, enhancing metabolic health, and supporting nerve regeneration, positioning it as a primary therapeutic countermeasure.

The challenge of severe genetic pathology is also addressed via the D2.mdx mouse model of Duchenne muscular dystrophy. Mattina et al. (2025) explore the impact of volitional exercise in this clinically relevant model, challenging concerns that exercise exacerbates the severe pathology. The study demonstrates that self-regulated wheel running safely augmented selective muscle mass and function, notably improving force production during taxing eccentric contractions and reducing fibrotic tissue. Mechanistically, this functional resilience is underpinned by improved mitochondrial health because volitional exercise normalized dystrophic skeletal muscle mitochondrial respiration and enhanced components of mitochondrial content and fusion. This provides strong preclinical evidence supporting the therapeutic value of prescribed aerobic activity in mitigating the myopathic decline in severe dystrophies. The companion journal club paper by Iasniswski et al. (2025) further emphasizes the clinical implications of these findings, suggesting that self-regulated movement, when carefully implemented, can be leveraged as a potent, safe therapeutic strategy in severe muscle wasting disorders.

Acute vulnerability: the physiological impact of disuse

Periods of physical inactivity, whether as a result of hospitalization, injury or forced rest, impose a potent and rapid physiological stress that mimics and often accelerates aspects of the ageing process. This special issue dedicates a section to characterizing the velocity and severity of these maladaptive responses to acute disuse.

The physiological cost of disuse is immediately apparent in the functional domain, as reviewed by Ruggiero and Gruber (2024). Their synthesis demonstrates that explosive strength, quantified as the rate of force development, decreases faster and to a greater magnitude than maximal strength during short-term unloading, indicating a disproportionate loss of functional power capacity. This disproportionate loss of rapid power capacity is underpinned by structural and neural changes. Motanova et al. (2025) used a 10 day bed rest model in elderly males to show that this acute stress rapidly exacerbates neuromuscular junction instability, resulting in reduced presynaptic/postsynaptic terminal overlap (a denervation signature) and decreased motor unit firing rate. This combination of compromised neural drive and muscle architecture severely limits the ability to generate the ballistic, high-velocity forces required for protective actions. The significance of these rapid, disuse-induced changes is further underscored by its immediate selection for an accompanying journal club paper (Abdalla et al., 2025). The consequence of this structural and neural deconditioning is a profound degradation of postural control, as detailed by Ritzmann et al. (2025). Their scoping review attributes the significant impairments in static, dynamic and anticipatory balance mainly to altered sensorimotor function, rather than solely to muscle strength loss. They present evidence for changes at the spinal level (e.g. reduced excitability of the monosynaptic stretch reflex) and at the supraspinal level (structural and functional changes in the sensorimotor cortex and cerebellum), together with a maladaptive reinterpretation of proprioceptive, vestibular and visual cues. These integrated neural deficits account for the increased sway and elevated fall risk observed after periods of inactivity.

Pathways to resilience: interventional physiology and positive plasticity

The most compelling aspect of this issue lies in the articles demonstrating the remarkable capacity for plasticity and resilience within the NMS, particularly when subjected to targeted physiological or nutritional interventions.

The translational promise of dietary nitrate supplementation is explored in two contributions. Rossi et al. (2025) provide mechanistic evidence that nitrate supplementation in aged mice reverts age-related alterations of neuromuscular junction morphology and enhances the anabolic Akt/mTOR pathway by increasing the expression of downstream factors. Furthermore, nitrate mitigated redox unbalance by increasing glutathione peroxidase content and reducing mitochondrial hydrogen peroxide production. An additional journal club article (Bisht et al., 2025) provides further context on the broad impact of nitrate on age-associated neuromuscular outcomes.

The discussion of high-performing models of resilience involves Zange et al. (2025), who employ magnetic resonance imaging to explore the muscle-specific effects of ageing and sport in Masters athletes. They found that intensive sprint and jump training largely compensates for age-related deficits in hip and leg muscle volume but does not prevent age-related increase in muscle fat fraction (myosteatosis) or the significant reduction in the intrinsic power-generating potential (sarcosthenia). The age-related loss of power is primarily attributed to sarcosthenia, which could not be explained by the fat fraction increase. Their findings are tempered by a critical commentary (Greyvenstein et al., 2025) that questions whether Masters athletes represent the universal gold standard for healthy ageing, urging caution in generalizing these specific adaptations.

Plasticity of the CNS can be non-invasively induced via paired corticospinal-motoneuronal stimulation (PCMS). Bjørndal et al. (2025) show that PCMS can enhance ballistic motor learning and induce robust corticospinal plasticity in older adults. Although older adults exhibit inferior baseline ballistic motor performance and significantly lower long-term retention compared to younger counterparts, a single session of PCMS reinstated this otherwise absent long-term retention. This outcome is further interpreted in a perspective article, which emphasizes that combining skill practice with targeted stimulation effectively boosts adaptations and overcomes age-related deficits in CNS plasticity (Taube, 2025). PCMS works by timing

transcranial magnetic stimulation to reach the corticomotoneuronal synapse before the peripherally-evoked antidromic volley, exploiting spike-timing-dependent plasticity to strengthen this critical synaptic pathway. This process acutely increases corticospinal excitability and primes subsequent motor practice, offering a sophisticated strategy to reboot the brain's capacity for motor learning and counteract the age-related decline in high-velocity force production.

Advancing methodological frontiers for integrated physiology

The physiological insights presented in this special issue are supported by ongoing advances in non-invasive measurement techniques. The review on human brain imaging with high-density electroencephalography (HD-EEG): techniques and applications (Marino & Mantini, 2024) is particularly pertinent. Standard EEG provides high temporal resolution but has poor spatial localization. The development of HD-EEG systems, combined with anatomically informed head models and advanced source-localization algorithms, has turned this limitation into an opportunity. By incorporating realistic representations of head anatomy and tissue conductivities, HD-EEG achieves fine spatial precision at the same time as retaining the millisecond temporal resolution characteristic of electrophysiological methods.

This integration bridges the gap between traditional EEG and other neuroimaging modalities such as functional magnetic resonance imaging, offering a more comprehensive view of the spatiotemporal dynamics of neural activity. As Marino and Mantini (2024) note, HD-EEG now enables the reconstruction of cortical generators at the source level, enabling detailed analyses of neural activity and connectivity that were previously unattainable with scalp-level recordings alone. Such methodological advances not only deepen our understanding of sensory, motor and cognitive processes, but also enhance the ability to study physiological mechanisms in clinical and applied contexts.

Particularly promising is the potential for HD-EEG to be combined with peripheral physiological measures, such as electromyography, kinematic data and cardiovascular monitoring, to investigate brain–body interactions in a truly integrative manner. This approach reflects the growing emphasis in integrated physiology on multiscale coupling, from neuronal oscillations to systemic responses. By enabling the simultaneous mapping of cortical dynamics and peripheral outputs, HD-EEG exemplifies the new frontier of non-invasive human physiology: dynamic, multimodal and mechanistically grounded.

Concluding remarks

This special issue offers a panoramic yet detailed view of the adaptive landscape of the NMS and CNS. It confirms the profound physiological costs associated with ageing and disuse, reinforcing the understanding that the motor unit is susceptible to rapid and systemic degradation. Crucially, however, these contributions offer powerful evidence of the inherent plasticity of the system. From the molecular stabilization offered by nutritional strategies to the synaptic strengthening achieved via neuromodulation, the papers gathered here lay down a comprehensive blueprint for future research. They emphasize that the motor system is not simply declining, but is a dynamic structure awaiting targeted intervention. The path forward demands sophisticated, integrated science that translates these fundamental mechanistic discoveries into effective strategies for maintaining human vitality and autonomy.

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