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Steven J. O'Bryan[1] and Danielle Hiam[2]

[1]*Institute for Health and Sport (IHeS), Victoria University, Melbourne, Australia*

[2] *Deakin University, Geelong, Australia, Institute for Physical Activity and Nutrition (IPAN), School of Exercise and Nutrition Sciences*

Corresponding author
Steven J. O'Bryan

Email: steven.obryan@vu.edu.au

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Introduction

Age-related reductions in muscle strength and muscle mass respectively equate to 1 - 4% and 1 - 2% annually from the age of 65. Similarly, maximum shortening velocity of the muscle fibres decreases by 15 - 40 % in older adults when compared to younger adults (Hunter *et al.*, 2016; Tieland *et al.*, 2018). These reductions in muscle mass and function are exacerbated in lower-limb muscles, and ultimately decrease the rate of force development, power production and the capacity to perform functional tasks such as walking, climbing stairs and rising from a chair. Fatigue development during moderate-high velocity dynamic contractions, generally performed during functional tasks, is also more severe in older compared to younger adults (Hunter *et al.*, 2016). A myriad of implications ensue, including increased fall and fracture risk, decreased independence, reduced quality of life and increased risk of mortality. The detrimental effects of ageing on physical function are influenced by biological changes influencing the activity of the motor unit, which consists of the alpha motoneuron in the spinal cord, its peripheral axons and its innervated muscle fibres (Figure 1).

Cortical motoneurons, which reside in the precentral gyrus of the frontal lobe and provide excitatory input to alpha motoneurons, experience considerable atrophy across the lifespan (Tieland *et al.*, 2018). Moreover, weaker older adults display considerably less cortical excitability and greater cortical inhibition compared to younger adults (Tieland *et al.*, 2018). At the spinal level, motoneuron death is thought to occur upstream from degeneration at the neuromuscular junction and peripheral axons, and affects more high threshold motoneurons (Hunter *et al.*, 2016). Although the precise mechanism of this degeneration is unclear, age-related oxidative stress may decrease the integrity of pre-synaptic terminals and the size, number and density of postsynaptic motor endplates, whereas inflammatory cytokines may impair motoneuron/myelin regeneration (Hunter *et al.*, 2016). Although inter-muscular and task-specific differences may exist, changes in neural structure can reduce the excitation and firing rates of motoneurons and the conduction velocity and stability of post-synaptic potentials (Hunter *et al.*, 2016; Tieland *et al.*, 2018).

Downstream from the neuromuscular junction, muscle fibres undergo their own form of degeneration into old age. Infiltration of non-contractile adipose and fibrous tissue decreases muscle fibre quality, and a larger degree of senescence and atrophy in type II compared to type I fibres leads to a higher type I:II fibre type ratio (Hunter *et al.*, 2016; Tieland *et al.*,

2018). Further, a reduction in the quantity of calcium release units and uncoupling between DHPR and RyR1 receptors negatively influences calcium handling and excitation-contraction coupling (Michelucci *et al.*, 2021). Type II fibre atrophy likely evolves from motor unit remodelling and/or reduced number of satellite cells necessary for the production and regeneration of myonuclei, whereas impaired calcium handling is largely mediated by mitochondrial dysfunction and increased oxidative stress (Michelucci *et al.*, 2021). Overall, these changes in the structural and intrinsic properties of the muscle fibre in old age decreases the strength and speed of the cross-bridge shortening cycle.

Long term physical activity is a cost-effective and non-pharmacological approach to limit the functional burden of ageing. Numerous systematic reviews and meta-analysis of randomised controlled trials have demonstrated the beneficial effects of primarily progressive resistance-based exercises on improving muscle strength in older adults, whereas increases in muscle power seem mediated by exercises involving high velocity muscle contractions (Straight *et al.*, 2016). Cross-sectional studies comparing highly trained older adults with age-matched sedentary controls suggest that superior levels of muscle strength and power may be explained by reduced type II muscle fibre atrophy and motor unit loss in old age (Hunter *et al.*, 2016). Others have reported that 12 weeks of heavy progressive resistance exercise increases satellite cell content in old (~70 years) but not very old (> 80 years) adults (Karlsen *et al.*, 2019). However, less is known of the effects of lifelong recreational physical activity on structural and functional changes in old age, which is of higher relevance to a greater proportion of the ageing population and may provide evidence for earlier intervention for neuromuscular dysfunction.

Can lifelong recreational physical activity offset neuromuscular dysfunction in old age?

A recent article published in the *Journal of Physiology* by Soendenbroe *et al.* (2022) aimed to determine the effects of lifelong physical activity on structural and functional changes in muscle. Three groups of male participants were compared, including young sedentary (n = 15; age range = 20 – 36 yrs), old sedentary (n = 15; age range = 68 – 82 yrs) and old physically active (n = 16; age range = 68 – 82 yrs) adults. Fibre denervation and satellite cell quantity and function were analysed using immunohistochemistry and reverse transcription quantitative polymerase chain reaction (RT-qPCR). Muscle function was assessed via

unilateral maximal voluntary contraction of the knee extensors (maximal torque and rate of torque development at 30˚/s) before and after a high-intensity concentric and eccentric exercise bout. Finally, dual energy x-ray absorptiometry (DEXA) scans assessed differences in body composition. It was hypothesized that although neuromuscular structure and function would decline with age, physically active older adults would exhibit more positive indices of muscle fibre and satellite cell content, and a superior functional profile compared to sedentary older adults.

The older cohorts displayed a lower cross-sectional area of type II muscle fibres and a higher percentage of muscle fibres displaying denervation (as assessed by $NCAM^+$ and $MyHCn^+$ expression) compared to the young sedentary group. Physically active older adults had a larger proportion of type I muscle fibres and greater type II muscle fibre satellite cell content compared to the old sedentary group. Lifelong exercise did not seem to ameliorate denervation of muscle fibres as there was no differences between the older physically active and sedentary cohorts. At the gene expression level, however, a similar expression profile of AChR was found between the physically active older adults and the young sedentary cohort. Altogether, the authors speculated that lifelong exercise may result in preserved satellite cell content near type II muscle fibres and the potential to mount a greater myogenic response in the event of fibre injury or denervation.

Compared to young, older adults exhibited a lower maximal voluntary torque, rate of torque development and lean body mass, but no significant effects of lifelong physical activity on these outcomes were identified. During high-intensity exercise, physically active older adults maintained a higher relative torque level compared to both sedentary groups. The authors concluded that although their assessment method may not have permitted detection of the beneficial effects of lifelong physical activity on neuromuscular function, superior performance during high-intensity exercise was indicative of greater fatigue resistance.

Future directions

Although maximal force generated during isometric or slow isokinetic contractions is a standard method for assessing neuromuscular function, assessment of force production at moderate-high velocities (i.e., power) may prove more accurate. As such, future research may benefit from assessing the force-velocity and power-velocity relationships of lower-limb muscles using either dynamometry or lower-limb dynamic tasks (e.g., cycle ergometry, leg

press, vertical jump) to better detect the effects of age and physical activity on neuromuscular function. Experimental techniques such as peripheral nerve and transcranial magnetic stimulation coupled with electromyography provide insight into the neural and muscular control of force and power production and may also be useful to associate structural and functional changes with age. Moreover, it is essential that older and sedentary adults unaccustomed to producing high intensity efforts are fully familiarised with the prescribed physical activity, as large heterogeneity in neuromuscular structure and function, as well as motivation, decreases the reliability of the outcomes (Hunter *et al.*, 2016).

As highlighted by Soendenbroe *et al.* (2022), the inclusion of males only is a limitation of their findings. This is a broad issue that is receiving increasing attention due to notable differences in female morphology and physiology when compared to males (Landen *et al.*, 2021). For example, compared to males, females have a smaller type I and type II muscle fibre cross sectional area, exhibit different motor unit firing patterns, have a lower type II muscle fibre satellite cell content, and display fibre-type specific satellite cell distribution not exhibited in males (Horwath *et al.*, 2021; Landen *et al.*, 2021). These differences in baseline muscle phenotype result in divergent muscle adaptation to a stimulus (i.e. exercise) and potentially different mechanisms of muscle ageing. With advancing age, females lose a comparable amount of lower-limb strength, but less muscle mass compared to males, suggesting differences in muscle quality and/or neural function. In addition to sex differences, there is currently a lack of evidence of the effects of the menstrual cycle on physical function in younger females and menopause on neuromuscular function in older females. Whether older physically active females demonstrate similar or different innervation and satellite cell profile to older physically active males provides an interesting opportunity for future research.

Conclusion

The decline in neuromuscular structure and function into old age may be mitigated by lifelong physical activity and the implementation of effective training programs. The work by Soendenbroe *et al.* (2022) conducted on males provides evidence that physically active older adults possess an innervation and satellite cell profile that is superior to sedentary older adults and comparable to young sedentary adults. Future research should build on these findings to further investigate the links between neuromuscular structure and function

with physical activity into old age, particularly during high velocity contractions, and include female participants.

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Additional information

Competing interests
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Author contributions
SO conceived the idea for the manuscript and prepared the figure. SO and DH drafted the manuscript, revised the manuscript for important intellectual content, and approved the final version of the manuscript.

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Figure 1. Summary of the general effects of age on the structure and function of the neuromuscular system. Physical activity has the potential to offset neuromuscular dysfunction in old age, although more research is required to determine optimal prescription guidelines and to link structural changes with clinically meaningful functional outcomes, particularly in female cohorts.

Figure 1.