OPINION

Muscle memory theory: Implications for health, athletic performance and sports integrity

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Introduction

Maintaining optimal levels of skeletal muscle mass (and strength) is a cornerstone for both health and performance not only because of its widely known role in functions such as locomotion, but also as a result of less popular effects, such as its role in metabolism (Severinsen & Pedersen, 2020). For this reason, strategies aimed at enhancing or preserving skeletal muscle throughout its lifespan should be a priority, and efforts are needed to fully understand the physiological mechanisms involved in skeletal muscle mass regulation.

Controversy exists, however, on the physiological processes underlying skeletal muscle hypertrophy/atrophy (Snijders et al., 2020). For decades, it has been postulated that an approximate linear relationship exists between muscle fibre size/volume and total number of muscle fibre nuclei (myonuclei). Thus, it was hypothesized that every myonucleus holds jurisdiction over a certain area of the muscle fibre cytoplasm (known as myonuclear domain), which would remain constant despite changes in muscle fibre size as a result of the addition of new myonuclei during periods of hypertrophy (supplied by muscle satellite cells) or the loss of myonuclei (apoptosis) during periods of muscle atrophy (Snijders et al., 2020). However, a growing number of studies have shown that myonuclei may not be lost during muscle atrophy (at least in the short to middle term), which would potentially facilitate muscle remodelling during a subsequent training period (Snijders et al., 2020). These findings have led to the so-called muscle memory theory, comprising the phenomenon whereby muscles could retain a form of ‘memory’ from previous training, allowing for faster remodelling (i.e. hypertrophy) after a period of detraining or disuse. This Opinion article aims to summarize current evidence on the muscle memory theory (with a particular focus on myonuclear permanence) in both animals and humans, as well as to discuss its potential relevance in different fields; from the long-term benefits of exercise training for the preservation of muscle remodelling capacity in older ages or after a disuse period, to the implications for sports integrity, particularly regarding potential lifelong benefits of doping strategies or the participation of transgender athletes in women’s sports.

Scientific evidence on the muscle memory theory

Current scientific evidence regarding the muscle memory theory is mostly supported by animal data. Bruusgaard & Gundersen (2008) observed no changes in myonuclear content even after 50% muscle atrophy induced via denervation in adult mice. Jackson et al. (2012) also observed that myonuclear content remained constant in mice soleus despite a 29% reduction in fibre cross-sectional area (CSA) after 14 days of hindlimb suspension. Of note, this persistence of myonuclear content enabled rapid regrowth of the muscle after a subsequent reloading period, even in muscles in which satellite cells had been depleted, which might reinforce the role of myonuclei (and not necessarily satellite cells) for muscle regrowth (Jackson et al., 2012). Another study in mice reported that cancer cachexia induced a marked atrophy of skeletal muscles (e.g. 21% in the extensor digitorum longus muscle) after 6 weeks, but no changes were again observed in myonuclear content (Winje et al., 2019). However, not all research has been conducted in rodents. In humans, Horwath et al. (2025) recently reported that 6 weeks of immobilization because of an Achilles tendon rupture led to no changes in the number of myonuclei despite a significant reduction in muscle fibre volume.

It is worth noting, nonetheless, that the results showing myonuclei permanence after periods of atrophy do not constitute per se an evidence-based explanation for the existence of skeletal muscle memory. However, preliminary evidence also suggests that the ‘surplus’ of myonyclei after periods of muscle atrophy could facilitate muscle remodelling during subsequent retraining periods. Two years after their first study on the topic, Bruusgaard et al. (2010) demonstrated that new myonuclei were added before increases in muscle size in response to an overload period in mice, and these myonuclei persisted after severe atrophy induced by denervation. Taking this concept one step further, the same research group used anabolic steroids to induce muscle hypertrophy in mice, which was associated with an increase in myonuclei (Egner et al., 2013). Interestingly, 3 weeks after steroid withdrawal, the myonuclear content remained 42% higher compared to the sham treatment group, whereas muscle fibre size had returned back to baseline levels (Egner et al., 2013). When overload was subsequently introduced for a 14 day period, the group who had undergone previous steroid treatment showed a muscle fibre hypertrophy response which was more than double compared to sham-treated mice (44% *vs.* 17%, respectively) (Egner et al., 2013). Moreover, Egner et al. (2013) repeated a similar experiment but, in this case, 3 months after steroid treatment, which represents ∼12% of mice lifespan (e.g. equivalent to a decade in a human). Again, the number of mionuclei remained higher (+28%) in the steroid group than in the sham group and, when mice were submitted to overload, a faster muscle growth was observed in the treated mice (+20% after 14 days) (Egner et al., 2013). Other studies have also reported findings that would support the muscle memory concept in rodents. For example, Lee et al. (2018) reported that the increase in myonuclear content observed after

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resistance training in rats was retained during a long-term detraining period (20 weeks), and this surplus of myonuclei seemed to assist with muscle hypertrophy and mitochondrial biogenesis following subsequent re-training. Thus, the muscle memory theory might not only benefit in recovering muscle mass, but also in mitochondrial biogenesis.

In humans, a recent study by Cumming et al. (2024) also seems to support the muscle memory theory, at least partly. Cumming et al. (2024) observed that a 10 week period of unilateral resistance training led to muscle hypertrophy as well as to an increase in myonuclear content. Following a 16 week detraining period, muscle size decreased, whereas myonuclear content persisted and remained 33% higher compared to the untrained arm (particularly in type 2 fibres) (Cumming et al., 2024). During a subsequent 10 week bilateral retraining period, a trend towards greater hypertrophy was observed in the previously trained muscle compared to the untrained one (particularly in type 2 fibres, 30% *vs*. 14% for the trained and untrained muscles). However, although the CSA of the trained muscle was significantly larger compared to that of the untrained one after the bilateral retraining period (+11.6%), differences in the delta change between arms did not reach statistical significance, and therefore the practical relevance of these findings should be interpreted with caution (Cumming et al., 2024).

Clinical implications of the muscle memory theory

Although further research is needed, if confirmed, the muscle memory theory could have important implications for health, particularly in the fields of healthy ageing or rehabilitation (Fig. 1*A*). Ageing is associated with declines in muscle mass. Moreover, older adults seem to present an impaired muscle remodelling capacity in response to resistance training compared to their younger peers (Brook et al., 2016). Although controversy exists (Brook et al., 2023), some reports suggest that this might be partly the result of a reduction in the number of satellite cells and myonuclear content (Karlsen et al., 2019). Indeed, Petrella et al. (2006) reported that older individuals present not only a blunted hypertrophy in response to a 16-week resistance training program compared to their younger peers, but also a reduced addition of myonuclei.

The muscle memory theory supports that the number of myonuclei overall reflect the largest size the muscle fibres have had throughout their lifespan. Thus, it might be hypothesized that exercise training at younger ages (with the subsequent muscle hypertrophy) could result in a higher myonuclear content at older ages, which might facilitate skeletal muscle remodelling and aid in the prevention of sarcopenia. Evidence in humans is lacking in this regard. However, preliminary evidence in rodents seems to support this hypothesis. Eftestøl et al. (2022) observed that 5 weeks of resistance (climbing) exercise induced an increase in fibre CSA and myonuclear content in young rats (age of 4 weeks). Although the benefits on CSA were lost after a 10 week detraining period, the myonuclear content remained constant. Moreover, when these rats were again submitted to another retraining period for 2 weeks, they showed a greater hypertrophic response (+16%) compared to rats who had previously performed no resistance exercise (Eftestøl et al., 2022).

If the concept of myonuclear permanence in the human skeletal muscle during ageing was confirmed to be true, this would underscore the importance of exercise training during youth for maximizing

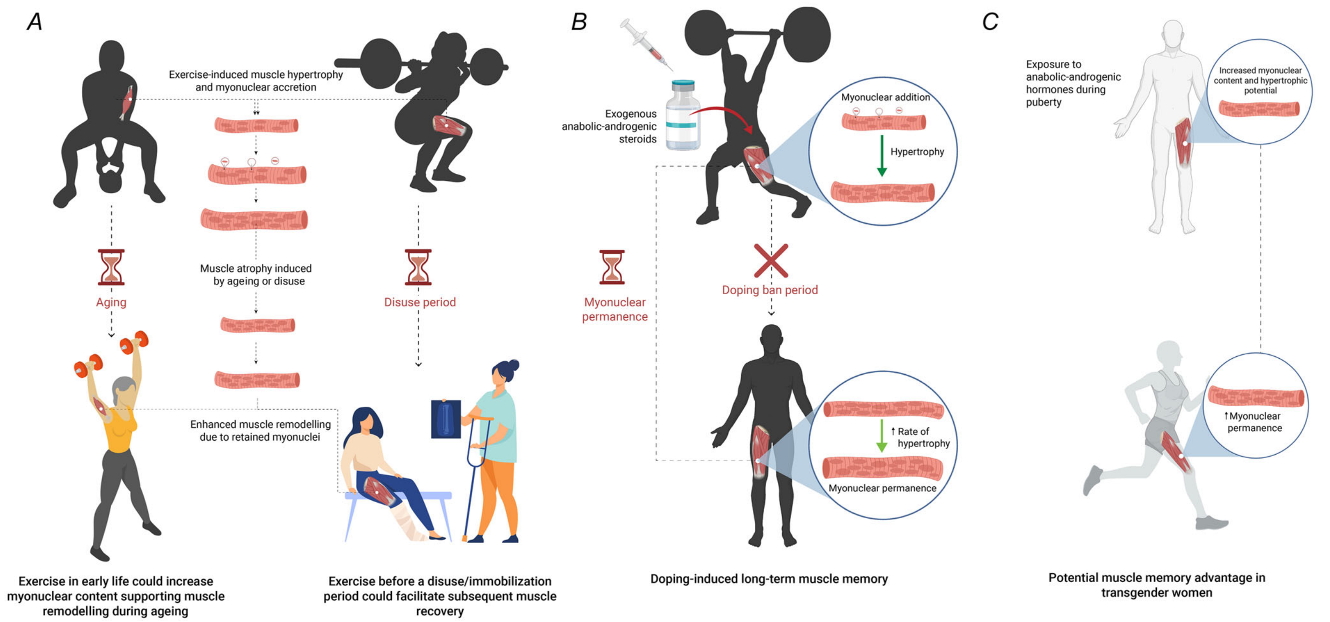

Figure 1. Potential implications of the muscle memory theory in different contexts
A, a high myonuclear content as a result of previous resistance training experience could enhance muscle remodelling capacity during ageing or after disuse periods. *B*, the increase in myonuclear content as a result of exogenous anabolic steroids could be a long-term advantage for doped athletes. *C*, the higher myonuclear content associated with exposure to endogenous androgenic hormones during puberty could result in a physiological advantage for trans women athletes competing in female categories.

muscle sensitivity to resistance exercise in older ages, which can have implications for health and performance. This would also translate into an enhanced ability to recover from muscle atrophy following immobilization or disuse periods because of injuries, surgeries or illnesses, which could be of relevance even in young adults. Further evidence is, however, needed in this regard. Indeed, a recent study reported a similar atrophy in response to 14 days of immobilization in formerly trained and untrained young individuals, as well as a similar hypertrophy (or even greater in formerly untrained individuals) after a subsequent 8 week resistance training period (Max Michel et al., 2025). However, it is worth noting that, although formerly trained individuals had no enhanced responsiveness to a subsequent training period, they had a larger muscle size throughout the study compared to the untrained individuals, thus supporting the beneficial effects of exercise training before a disuse period (Max Michel et al., 2025). Whether these effects could differ in older adults remains unknown, but it might be hypothesized that lifelong training could create a physiological reserve that would be beneficial to prevent reaching excessively low levels of muscle mass as a result of ageing or disuse.

Skeletal muscle memory and its implications for fairness in sports: should lifelong doping sanctions be applied?

The skeletal muscle memory theory could also have important implications for a contentious topic in sports such as doping bans, particularly regarding anabolic steroids use (Fig. 1*B*). Anabolic androgenic steroid doping results in increased lean body mass and muscle strength, and for this reason these substances are banned with sanctions of up to 4 years (although duration might depend on several factors). However, according to the muscle memory theory, the benefits of anabolic steroids could be long-lasting because these substances could increase muscle size and myonuclear content, with the latter remaining even after long-term remission of anabolic steroids use and subsequent atrophy.

Confirming the abovementioned theory, powerlifters who had taken anabolic steroids for ∼10 years show a larger muscle fibre size and a greater myonuclear content than their peers who had never taken these substances (Eriksson et al., 2005). Similarly, Nielsen et al. (2023) found a higher myonuclear density in strength-trained individuals who had stopped using anabolic steroids ∼4 years before compared to a control group who had taken no anabolic steroids, with myonuclear density being positively correlated with the number of weeks during which participants had taken anabolic steroids. Moreover, although both groups had a similar strength training frequency, those individuals who had used anabolic steroids had greater muscle mass and maximal strength than controls, which reinforces the practical implications of these findings (Nielsen et al., 2023). A recent study by Lima et al. (2023) also seems to support this notion. Lima et al. (2023) observed that, in resistance-trained individuals who had taken anabolic steroids, fibre CSA decreased after cessation of drug usage for ≥18 weeks. However, the number of myonuclei per fibre remained similar or even increased between visits in one subject (Lima et al., 2023).

Thus, these findings suggest that doping with anabolic steroids could induce long-term increases in myonuclear content. Although further research is needed, attending to the abovementioned studies in humans (Nielsen et al., 2023) and rodents (Egner et al., 2013), this might enhance retraining/muscle remodelling capacity even more than 4 years after doping cessation, thus supposing a long-term advantage for doped athletes and opening the door to lifelong sanctions. Moreover, it is worth noting that, although many studies on this topic have applied a detraining protocol after cessation of anabolic steroids use, in the case of athletes subjected to a doping sanctions, it is possible that they keep training, potentially leading to a higher likelihood of retaining the adaptations. Thus, the time course of these changes after doping cessation should be determined in future studies.

Skeletal muscle memory and the case of transgender athletes

The abovementioned findings could also have implications for a timely debate in sports, such as the participation of transgender athletes in women's events. In recent years, different studies have supported the prohibition of transgender athletes from participating in a wide range of strength and endurance sports, primarily justified by the higher testosterone levels (among other androgenic characteristics) observed in these populations, which might be associated with increased performance and potentially to a higher sensitivity to training-induced adaptations (e.g. muscle mass gains) (Hilton & Lundberg, 2021). However, trans women athletes have been reported to present a higher performance in some events even after 1 year of testosterone suppression (Roberts et al., 2021).

In this regard, it has been proposed that some of the 'advantages' of trans athletes on performance might be derived by the higher amount of androgenic hormones during puberty (Hilton & Lundberg, 2021). Attending to the abovementioned preclinical and clinical studies showing increases in myonyclear content with exogenous androgenic steroids (Egner et al., 2013; Nielsen et al., 2023), it could be hypothesized that the exposure of trans women athletes to androgenic hormones during puberty could potentially exert long-term benefits related with the muscle memory theory (Fig. 1*C*). Males have been reported to present a greater hypertrophic response to resistance training compared to females, as well as a higher number of myonuclei per fibre (even at the oldest ages, i.e. >80 years) and a trend towards a higher addition of myonuclei with resistance training (Karlsen et al., 2019; Petrella et al., 2006). Evidence is needed to confirm whether differences exist in myonuclear content between trans women and cis women athletes, as well as to determine when these differences emerge, and if the potential differences are reduced after gender affirming hormone therapy. However, if the theory of skeletal muscle memory is confirmed, trans women athletes, especially those who transitioned after puberty, could be in a position of competitive advantage over cis women because of the potential effects of testosterone and other androgens on the skeletal muscle during the years preceding their transition.

Perspectives and conclusions

Despite the abovementioned findings, caution is warranted as controversy exists regarding the existence of the muscle memory theory, particularly in humans. For example, a study by Blocquiaux et al. (2020) reported that, after an initial 12 week period of resistance training-induced hypertrophy, a 12 week detraining period caused muscle atrophy along with a trend towards a reduction in myonuclear number, which was again recovered after 12 weeks of retraining. These findings would refute the muscle memory theory, and suggest that myonuclear domain remains overall constant (with the number of myonuclei decreasing concomitantly with fibre size) (Blocquiaux et al., 2020). Moreover, numerous research gaps need to be addressed. It might be hypothesized that muscles could retain training-induced myonuclei but not permanently, but the time course of these changes remains unknown. Similarly, different disuse models could elicit different effects at the myonuclear level, and it might be hypothesized that greater levels of atrophy could lead to losses in myonuclear content. Finally, it should be noted that, although the focus regarding the muscle memory theory has been mostly placed on the persistence of myonuclei, other mechanisms, such as the existence of an epigenetic memory after periods of exercise training, could also play a role in both animals and humans.

In summary, although there is still no consensus within the scientific community regarding the existence of muscle memory, growing observational and experimental evidence in animals and humans suggests that myonuclear content could be retained during disuse periods, which might enhance exercise responsiveness during a subsequent retraining period. This would also support the importance of exercise training during youth to prevent ageing-related muscle loss. Moreover, evidence suggests that exogenous anabolic steroids could induce long-lasting beneficial effects at the muscle level, opening the door to lifelong sanctions. Finally, exposure to androgenic hormones during puberty could potentially exert long-term benefits related with the muscle memory theory in trans women athletes, which is of relevance from the perspective of fairness in sport.

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No competing interests declared.

Author contributions

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Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the HTML view of the article. Supporting information files available:

Peer Review History