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TOPICAL REVIEW

Ageing reduces persistent inward current contribution to motor neurone firing: Potential mechanisms and the role of exercise

Lucas B. R. Orssatto¹, Anthony J. Blazevich²  and Gabriel S. Trajano³ 

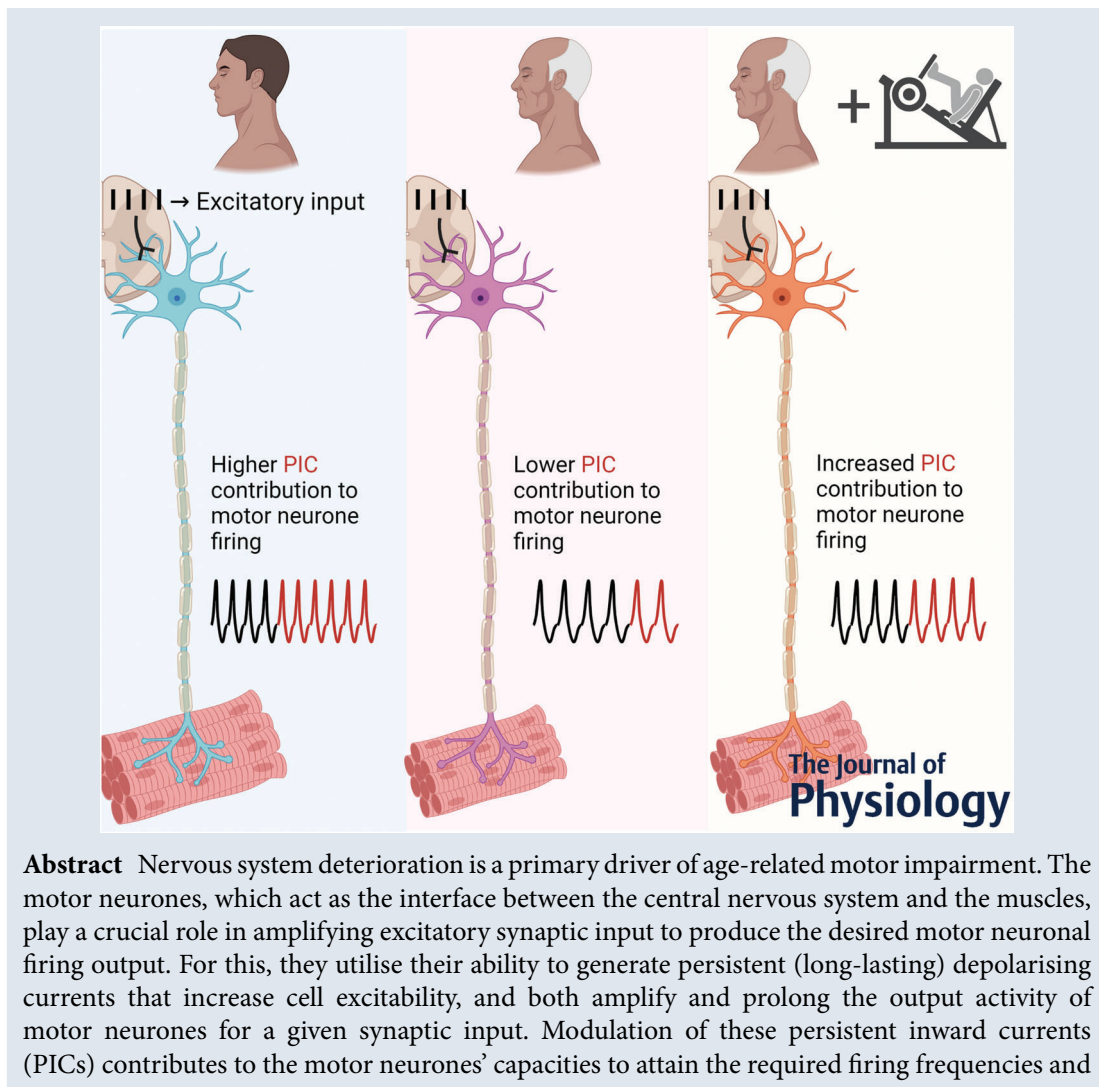
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Abstract Nervous system deterioration is a primary driver of age-related motor impairment. The motor neurones, which act as the interface between the central nervous system and the muscles, play a crucial role in amplifying excitatory synaptic input to produce the desired motor neuronal firing output. For this, they utilise their ability to generate persistent (long-lasting) depolarising currents that increase cell excitability, and both amplify and prolong the output activity of motor neurones for a given synaptic input. Modulation of these persistent inward currents (PICs) contributes to the motor neurones' capacities to attain the required firing frequencies and

rapidly modulate them to competently complete most tasks. Thus, PICs are crucial for adequate movement generation. Impairments in intrinsic motor neurone properties can impact motor unit firing capacity, with convincing evidence indicating that the PIC contribution to motor neurone firing is reduced in older adults. Indeed, this could be an important mechanism underpinning the age-related reductions in strength and physical function. Furthermore, resistance training has emerged as a promising intervention to counteract age-associated PIC impairments, with changes in PICs being correlated with improvements in muscular strength and physical function after training. In this review, we present the current knowledge of the PIC magnitude decline during ageing and discuss whether reduced serotonergic and noradrenergic input onto the motor neurones, voltage-gated calcium channel dysfunction or inhibitory input impairments are candidates that: (i) explain age-related reductions in the PIC contribution to motor neurone firing and (ii) underpin the enhanced PIC contribution to motor neurone firing following resistance training in older adults.

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Abstract figure legend Motor neurones – the final common pathway to the muscles – accelerate, amplify and prolong their output activity, for a given synaptic input, by generating persistent inward currents (PICs). PIC modulation enables motor neurones to achieve the necessary firing frequencies to successfully accomplish various motor tasks. There is convincing evidence that PICs contribution to motor neurone firing is reduced with ageing. The motor neurone PIC-related amplification for a given synaptic input in young and older adults, as well as older adult after resistance training, is illustrated. The young adult motor neurone fires at a higher frequency and displays longer firing hysteresis (i.e. input–output gain) than the older adult because of higher PIC magnitudes. In turn, the older adult presents increased firing frequencies and longer firing hysteresis after resistance training, resulting from increased PIC magnitude.

Introduction

Nervous system deterioration is a critical factor driving ageing-dependent motor impairment (Orssatto et al., 2018). Muscle force control requires appropriate levels of synaptic input to be delivered from the central nervous system to the motor neurones, the final common pathway to muscle (Sherrington, 1906). The motor neurones themselves are subsequently responsible for integrating and modulating excitatory synaptic input to evoke an appropriate motor neurone (and thus motor unit) firing output (Heckman & Enoka, 2012). Age-related structural and functional alterations observed within the motor neurones are therefore consistent with findings that motor

neurones of older adults fire at lower frequencies than young adults, at least as observed in several muscles (Orssatto, Borg, Pendrith et al., 2022), as well as a reduced ability to rapidly increase motor unit firing frequencies in response to increased force requirements (Klass et al., 2008).

Because age-related alterations in intrinsic motor neurone properties impact motor unit firing capacity, the contribution of persistent inward currents (PICs) to motor neurone firing modulation, an essential intrinsic cellular property, could be affected and thus may play a major role in the observed motor impairment. PICs are depolarising currents generated by specialised voltage-sensitive sodium and calcium channels that

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increase cell excitability, accelerating, amplifying and prolonging the output activity of motor neurones for a given synaptic input (Heckman et al., 2005). Under conditions of high monoaminergic drive (including serotonergic and noradrenergic drive in the spinal cord), PICs can amplify synaptic input by as much as five-fold (Lee & Heckman, 1996, 2000). Several lines of evidence suggest that PIC modulation works in concert with task demand, contributing to motor neurone firing frequency adjustments to attain the level of force required to complete the task (Heckman, 1994; Heckman & Binder, 1991; Huh et al., 2017; Orssatto, Mackay et al., 2021; Powers et al., 2008). This additional current derived from PICs promotes an input–output hysteresis in motor unit firing (Powers & Heckman, 2015). Recent estimates of PIC-related motor neurone firing hysteresis in humans provide convincing evidence of a reduction in older adults (Guo et al., 2023; Hassan et al., 2021; Orssatto, Borg, Blazevich et al., 2021; Orssatto, Fernandes et al., 2022). This is consistent with findings in animal studies showing lower motor neurone excitability in aged populations (Kalmar et al., 2009; Morales et al., 1987), although net motor neurone excitability may also be regulated by other intrinsic properties. Thus, PIC alteration in older adults appears to be an important mechanism contributing to impairments in physical function, and thus presents a promising target for future intervention.

Direct motor neuronal PIC measurements can only be made in animal experiments using invasive procedures. In humans, PIC contributions to motor neurone firing can only be estimated non-invasively, typically by studying motor neurone firing hysteresis of pairs of motor units during voluntary contractions. This paired-motor unit analysis is used to calculate ΔF frequency (ΔF), comprising the level of recruitment–derecruitment firing hysteresis. ΔF reflects the prolongation caused by PICs, largely dependent on calcium-channels PICs (Fig. 1) (Afsharipour et al., 2020; Gorassini et al., 1998). Recent technological developments permit the non-invasive assessment of motor unit firing frequencies using high-density electromyography (Enoka, 2019; Farina et al., 2016; Holobar et al., 2014; Khurram et al., 2022). This technology creates a unique opportunity to investigate the effects of ageing on both the magnitude and facilitation–inhibition control of the PIC contribution to motor neurone firing, their adaptation to exercise and their influence on physical function. In this narrative review, we (i) present evidence for the negative influence of ageing on PIC contribution to motor neurone firing, including factors influencing their facilitation and inhibition; (ii) discuss the promising effects of exercise on PICs in older adults; and (iii) propose opportunities for future investigations on the topic.

Influence of ageing on motor neurone PICs

Many neural processes influencing the motor pathway are affected by ageing, from the generation of synaptic input to the firing frequency output of the motor units (Clark, 2023; Orssatto et al., 2018), and motor neurones are not spared. Motor neurones fire at slower frequencies in older adults than in young adults, and the magnitude of these differences increases with contraction intensity (Orssatto, Borg, Pendrith et al., 2022). This could be a consequence of functional and/or structural changes within the nervous system, including axonal demyelination, atrophy and degeneration (Orssatto et al., 2018). This deterioration can trigger muscle fibre denervation, resulting in some fibres being unable to contribute to force production (Aare et al., 2016). Although a compensatory mechanism allows low-threshold motor neurones to reinnervate some nearby denervated muscle fibres that were previously innervated by higher-threshold motor neurones, it does not prevent the reduction in motor unit firing frequency because the lower-threshold reinnervating motor neurones (Piasecki et al., 2016) will exhibit slower maximal firing frequencies (Orssatto, Borg, Pendrith et al., 2022). Indeed, deterioration of structure and function of motor neurones could be partially accountable for age-related reductions in motor neurone firing frequencies. A reduced PIC contribution to motor neurone firing is a novel

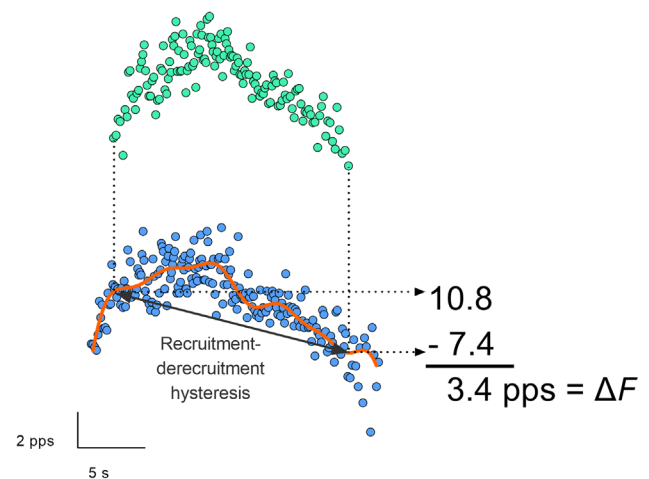


Figure 1. ΔF calculation

Test motor unit (top, green) and control motor unit (bottom, blue) firings obtained from the tibialis anterior of an older adult during a ramped contraction ($2\% \text{ s}^{-1}$ rate of torque rise and decline) up to 20% of the individual maximal force capacity, used for paired-motor unit analysis. This method calculates the level of recruitment–derecruitment firing hysteresis (calculated as ΔF), which is an estimate of the PIC contribution to motor neurone firing. The y-axis displays motor unit instantaneous firing frequencies (pps) and the x-axis shows time (s). Continuous estimates of motor unit firing frequencies (orange line) from the control unit were generated using support vector regression (SVR) (Beauchamp et al., 2022) and is a representation of synaptic input to the motor pool.

Table 1. Identified motor units and test units (used to calculate ΔF) per age group and muscle

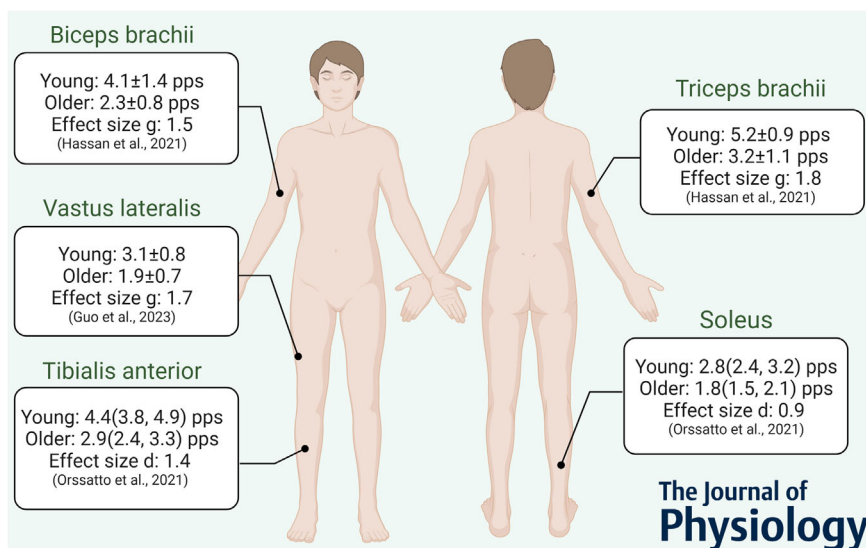
Muscle	Biceps brachii	Triceps brachii	Vastus lateralis	Tibialis anterior	Soleus
Young					
Motor units	6 ± 4	9 ± 5	18 ± 9	19 (16–23)	7 (5–8)
Test units	2 ± 1*	4 ± 3*	4 ± 2	11 (8–14)	5 (3–6)
Older					
Motor units	4 ± 2	7 ± 3	17 ± 3	20 (16–27)	8 (6–9)
Test units	2 ± 2*	5 ± 3*	3 ± 2	14 (9–18)	4 (3–6)
Desc stats	Mean ± SD			Median (first and third quartile)	
Study	Hassan et al., 2021		Guo et al., 2023	Orsatto et al., 2021	

ΔF , Δ frequency; Desc stats, descriptive statistics reported in the study. *Test units for Hassan et al. (2021) were obtained across several contraction trials and the displayed values are averaged per trial (young adults, biceps brachii: 25 ± 13 test units from 11 ± 2 trials and triceps brachii: 48 ± 35 test units from 11 ± 1 trials; older adults, biceps brachii: 31 ± 25 test units from 17 ± 7 trials and triceps brachii: 64 ± 44 test units from 17 ± 8 trials).

mechanism that partially underpins the lower firing frequency observed with ageing. Recent studies have reported smaller ΔF values in older individuals compared to young individuals in soleus, tibialis anterior, biceps brachii, triceps brachii and vastus lateralis muscles (Fig. 2 and Table 1) (Guo et al., 2023; Hassan et al., 2021; Orsatto, Borg, Blazevich et al., 2021), suggesting a clear reduction in the contribution of PICs to motor neurone firing in ageing.

It is important to note that ΔF values measured in humans can be influenced by both neuromodulation – mediated by activation of G protein-coupled receptors – and inhibition (Heckman et al., 2008). It has been suggested that neuromodulatory drive to motor neurones works as a gain system that increases with contraction intensity and contraction of unrelated muscles (Johnson & Heckman, 2014; Wei et al., 2014). Several recent studies quantified the level of ΔF neuromodulation capacity in older adults using a range of

paradigms. In one study, we found that ΔF values scaled linearly and positively with contraction intensity between 10% and 30% of maximum force in soleus motor units in younger adults (Orsatto, Mackay et al., 2021), but, in a follow-up study, we found no such effect of contraction intensity (20–40% of maximum) in untrained older adults (Orsatto et al., 2023). This might explain the lower firing frequencies relative to younger adults at higher intensities of contraction (rate code compression) (Barry et al., 2007), which is also consistent with reduced PIC-mediated amplification in motor neurone firing. The inability of older adults to increase ΔF with contraction intensity might suggest an impairment in serotonergic drive to the spinal cord. However, in a more recent study, we investigated whether a remote handgrip contraction, which is hypothesised to diffusely increase serotonin release into the spinal cord, could increase ΔF values in the soleus of older and younger adults (Orsatto, Fernandes et al., 2022). We found that the contraction

**Figure 2. ΔF in young and older adults**

The available data showing lower biceps brachii and triceps brachii (Hassan et al., 2021), vastus lateralis (Guo et al., 2023), and tibialis anterior and soleus (Orsatto, Borg, Blazevich et al., 2021) ΔF in older adults than in young adults. All data are derived from submaximal ramp-shaped contractions to 20% of each individual's maximal capacity.

increased ΔF values during a low-intensity contraction (i.e. 20% of maximal capacity) equally in both younger and older adults. This outcome suggests that the mechanisms of facilitation caused by the remote contractions were not affected by ageing and that PIC neuromodulation might not have been substantively impaired, although this remains to be tested in other muscles. It is also possible that the strong effect of the remote handgrip contraction on soleus and tibialis anterior ΔF values might be seen in the low-intensity contractions to 20% of maximum force but this may not be the case at higher contraction intensities. In future studies, it will be of interest to determine whether an age-related ceiling effect truly exists.

With regard to inhibition, inhibitory control of the PIC contribution to motor neurone firing in ageing was examined in the same study (Orssatto, Fernandes et al., 2022). Reciprocal inhibition induced by tibialis anterior tendon vibration reduced soleus ΔF in both younger and older adults, indicating a similar effect of Ia-reciprocal inhibition circuits on this muscle. However, after Achilles tendon vibration, the reductions observed in tibialis anterior ΔF were smaller in older than young adults, implying that ageing might affect the inhibitory control of PICs. Thus, there is conflicting evidence as to whether ΔF facilitation, possibly via monoaminergic input, is impaired in older adults, although it is clearer that inhibitory control of PICs is negatively affected by ageing, at least in some muscles (e.g. tibialis anterior). This is of practical importance because daily activities demand co-ordinated activation and inhibition across muscle groups for appropriate motor control and loss of this co-ordination might feasibly underpin age-related motor impairment, potentially reducing, for example, both functional capacity and balance in this population. It is worth considering that older adults present muscle-tendon unit alterations such as increased muscle fibre stiffness and reduced tendon stiffness (Orssatto et al., 2018). This could alter their response to vibration-induced reciprocal inhibition; hence, it is a confounding factor that should be considered when interpreting these findings.

Potential mechanisms underpinning reductions in PIC magnitude with ageing

Most of the available methods that directly assess the potential mechanisms underpinning age-related reductions in PIC magnitude are invasive. Thus, because it is not feasible to directly assess most of these mechanisms *in vivo* in humans, hypotheses can be drawn from animal experiments and indirect human measurements.

Motor unit firing frequencies are strongly influenced by serotonergic and noradrenergic release onto the

motor neurones through their modulating effects on PIC amplitudes (Heckman et al., 2005). Therefore, age-related decreases in monoaminergic input onto motor neurones might limit firing rates through PIC reduction. Decreased serotonin and noradrenaline concentrations have been observed in the brains of aged rats (Míguez et al., 1999). Although no human data exist, such findings are consistent with the deterioration of structural integrity (Liu et al., 2020) and a reduction in neuromelanin (a product of noradrenaline synthesis) content in noradrenergic neurons emanating from the locus coeruleus (Shibata et al., 2006), impairing noradrenaline secretion in older adults. Degeneration of serotonergic axons projecting to the ventral horn of the lumbar spinal cord, from which motor neurones innervating lower limb muscles emanate, has also been detected in humans (Johnson et al., 1993), affecting serotonergic drive onto the motor neurones. Additionally, increases in pro-inflammatory cytokine circulation (e.g. interleukin-6, tumour necrosis factor- α and C-reactive protein) observed during ageing (Michaud et al., 2013) may affect the sensitivity of serotonin receptors (Steinbusch et al., 2021). Thus, older adults might present reduced serotonin and noradrenaline receptor sensitivities to receive the already lower monoaminergic drive on the motor neurones, which would then impair the generation and subsequent modulation of PICs in this population.

Voltage-gated sodium channels and L-type voltage-gated calcium channels – widely present on the somatodendritic surfaces of motor neurones – are primary sources of PICs in human motor neurones (Heckman et al., 2005). Dysfunction and also reduced density, number and composition of these voltage-sensitive ion channels in the motor neurone with ageing could compromise the presence of PIC-related motor neurone firing-frequency acceleration and amplification, as well as firing hysteresis. This could be a consequence of ageing because of, for example, changes in neurotrophins/trophic signalling (Ulfhake et al., 2000) resulting from increased pro-inflammatory environment (Michaud et al., 2013). Another important mechanism that could reduce PIC contributions to motor neurone firing in older adults is an imbalance between excitatory and inhibitory input both to and within the motor neurones. PICs are highly sensitive to inhibitory inputs, as demonstrated in animal (Hultborn et al., 2003; Hyngstrom et al., 2008) and human experiments (Mesquita et al., 2022; Orssatto, Fernandes et al., 2022; Revill & Fuglevand, 2017). Ageing is accompanied by changes in the strength and/or pattern of inhibitory input onto motor neurones (Hortobágyi & Devita, 2006; Kido et al., 2004; Orssatto, Fernandes et al., 2022). Ageing progressively reduces excitatory synaptic inputs within the motor neurone soma and dendrites, resulting in motor circuitry with reduced excitatory and increased inhibitory synapses

(Castro et al., 2023). These alterations within factors could be critical in inhibiting PICs. The influence of inhibitory input on the PIC contribution to motor neurone firing could be further explored using common neurophysiological techniques; for example, by vibrating an antagonist tendon or electrically stimulating the antagonist muscle to generate reciprocal inhibition (Mesquita et al., 2022; Orsatto, Fernandes et al., 2022) or electrically stimulating the agonist muscle for recurrent inhibition (Özyurt et al., 2019). In summary and hypothetically, (i) reduced neuromodulatory drive onto and impaired monoaminergic receptors sensitivity in motor neurones; (ii) voltage-sensitive ion channel dysfunction; and (iii) altered inhibitory input onto motor neurones are critical candidates potentially underpinning age-related decreases in the PIC contribution to motor neurone firing, as presented in Fig. 3. However, it is important to note that the influence of each of these mechanisms on PICs remains to be explicitly tested in the future.

Effects of resistance training on PICs in older adults

Resistance training induces multiple adaptations within the aged nervous system (Walker, 2021). These neural adaptations regardless of age largely underpin the early increases in muscular strength in advance of substantial changes in muscle mass, and continuously contribute to subsequent increases in strength as the training progresses

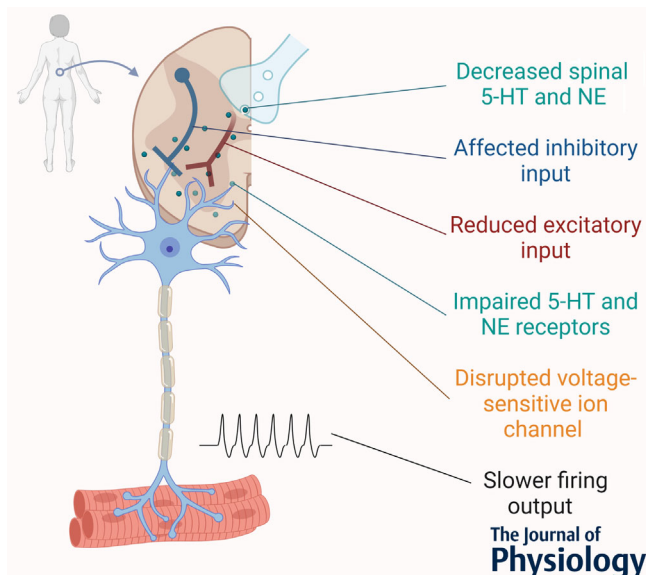


Figure 3. Potential mechanisms underpinning reductions in PIC magnitude during ageing

Decreased spinal serotonin (5-HT) and noradrenaline (NE), affected inhibitory input, impaired 5-HT and NE receptors, and voltage-sensitive ion channel dysfunction are possible candidates explaining the reduced PIC contribution to motor neurone firing during ageing, which should be explicitly explored in future studies.

(Pearcey et al. 2021). Recent animal (Krutki et al., 2017) and human (Orsatto et al., 2023) data suggest that increases in PIC magnitude observed after resistance training in older adults could be a mechanism underpinning the increases in motor unit firing frequencies, functional capacity and strength in this population. Krutki et al. (2017) studied the effects of resistance training on the properties of lower- and higher-threshold motor neurones using an animal model. They resistance trained the leg extensor muscles of young rats for 5 weeks as they lifted weights on their shoulders when reaching for food. After 5 weeks, motor neurones (i) needed lower currents to be recruited and to subsequently evoke rhythmic firing; (ii) fired at higher frequencies for a given current injection (i.e. increased frequency–current relationship slopes); and (3) produced higher steady-state firing frequencies. It is important to note that these results were more prominent in higher threshold motor neurones and indicate a clear adaptability of intrinsic motor neurone properties to resistance training, suggesting that enhanced PIC amplitudes might be evoked in response to the training. The same group of researchers conducted another study in which motor neurone properties were investigated before and both 5 and 12 weeks after gastrocnemius muscle overload was induced by tenotomy of

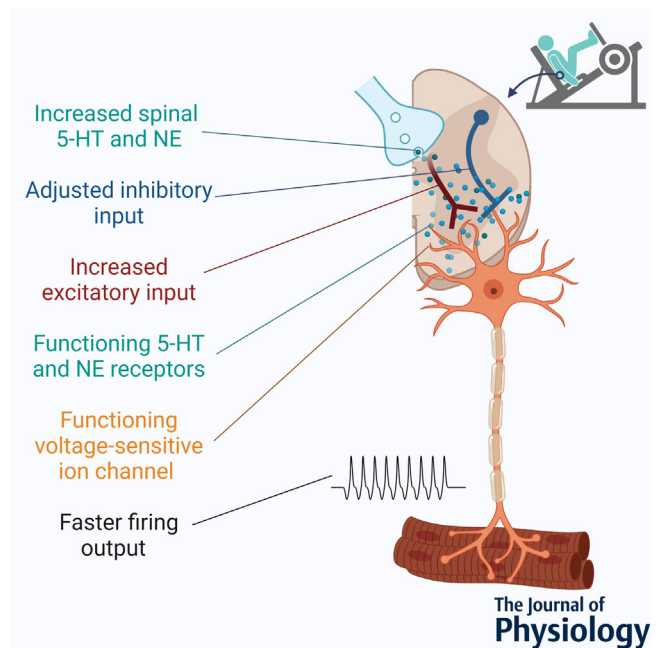


Figure 4. Potential mechanisms underpinning increases in PIC magnitude after resistance training in older adults

Increased spinal (5-HT) and noradrenaline (NE), adjusted inhibitory input, functioning 5-HT and NE receptors, and voltage-sensitive ion channel dysfunction are possible candidate mechanisms underpinning the increase in the PIC contribution to motor neurone firing in older adults, which should be explicitly explored in future studies.

the synergistic lateral gastrocnemius, soleus and plantaris muscles (Krutki et al., 2015). Although no changes were detected in lower threshold motor neurones, shortening of spike duration and rise time, an increased input resistance, and decreased rheobase were observed in higher threshold motor units. Additionally, higher-threshold motor neurones needed less current for steady-state firing to be evoked. This speculatively shows that PICs can be altered with exercise training, and potentially with resistance training, and this might also assist with the recruitment of higher threshold units, which are most susceptible to age-related dysfunction. Another possibility is that PIC activation thresholds could have been reduced by exercise, which could consequently increase the contribution of sub-threshold PIC to a lower motor neurone recruitment threshold. It is worth noting that Krutki et al. (2015, 2017) used anaesthetised preparations with minimal PICs, and this should be considered when interpreting their findings.

Such data from the animal model encouraged our group to investigate the potential changes in PIC contribution to firing in humans in response to training (Orssatto et al., 2023). We found increases in soleus ΔF values after 6 weeks of power-oriented resistance training in a group of older adults (>65 years). This was accompanied by an increased soleus ΔF as the contraction strength increased. Such results indicate not only that PIC contributions to motor neurone firing may be enhanced, but also that the ability to vary motor neurone input–output gain to increase muscle force production is improved with training – motor neurone input–output gain modulation therefore shifted towards a younger phenotype after the training. Potentially of similar interest, moderate-to-strong repeated-measures correlations (i.e. correlations across time points) were observed between changes in ΔF and increases in peak firing frequencies, maximal strength and functional capacity following resistance training. These correlations between change scores across multiple time points strongly point to (although do not prove) a causative effect of changes in ΔF on the changes in motor neurone firing and physical function. It is thus important that further studies attempt to repeat such findings in both similar and disparate populations. Regardless, the collective results of both human and animal studies suggest that adaptations to motor neurone properties (i.e. PICs) contribute to the increases in motor neurone firing output following resistance training in older adults, and this may be a potential mechanism underpinning increases in strength and motor function with training in this population. Notwithstanding, the evidence of increased PIC magnitude in animal (Krutki et al., 2017) and human (Orssatto et al., 2023) experiments may differ mechanistically. PICs generated by voltage-gated sodium channels may have contributed to the changes observed

in the animal experiments (Krutki et al., 2015, 2017). The sodium PIC is very fast activating; hence, it is essential for spike initiation and allowing repetitive firing (Heckman et al., 2005). Conversely, voltage-gated calcium channel PICs may have contributed to the changes observed in the experiment in humans because of the nature of the ΔF measurements. Calcium PICs are activated after recruitment and enable motor neurone self-sustained firing, prompting firing rate hysteresis (Heckman et al., 2005), which is measured by the ΔF technique (Powers & Heckman, 2015). Recent developments in the estimation of the PIC contribution to motor neurone firing rate acceleration (Beauchamp et al., 2023), along with ΔF calculations, will enable the investigation of resistance training-related adaptations on estimates of sodium and calcium PICs in future experiments.

The reasons for the greater PIC magnitude and its contribution to motor neurone firing following resistance training are yet to be elucidated. One possibility is that changes within the monoaminergic system might play a role. For example, increased levels of serotonin immunoreactivity have been observed in the hypoglossal nucleus of old rats after resistance training of the tongue, indicating a potential increase in serotonergic input onto motor neurones that innervate the trained genioglossus muscle (Behan et al., 2012). This is noteworthy because the PIC-related variable gain control system can amplify the net excitatory input based on the levels of serotonergic and noradrenergic input onto the motor neurones (Lee & Heckman, 2000). Another potential mechanism is an improvement in the regulation of neurotrophin signalling, which could contribute to possible changes in the density, number, composition or function of voltage-sensitive ion channels on the motor neurone (Gardiner, 2006). Somatodendritic sodium channels and L-type calcium channels generate motor neuronal PICs (Heckman et al., 2005). Although it is not feasible to measure channel properties in humans, previously discussed evidence from rats, such as enhanced sodium channel function or calcium channel modification leading to an increase in the steady-state firing frequency and minimal current amplitude required for depolarisation, suggests that resistance training may alter voltage-gated channels (Krutki et al., 2017). Lastly, decreases in inhibition after resistance training could also explain the increase in ΔF observed after resistance training. Although challenging to test in humans, future studies should investigate the hypotheses that (i) enhanced monoaminergic input onto motor neurones; (ii) changes in voltage-gated calcium channel density, number, composition and function; or (iii) reductions in inhibition, could lead to an enhanced PIC contribution to motor neurone firing following resistance training.

Different exercise modalities, including endurance training, might also hold promise based on data from

experiments in young animals and computational simulations (Power et al., 2022). For example, 3 weeks of treadmill training increased PICs in serotonergic neurons of the dorsal raphe nucleus in mice (Ge & Dai, 2020). These findings, combined with evidence indicating that almost all spinal-projecting serotonergic neurons are activated when animals engage in treadmill-induced locomotion (Schmidt & Jordan, 2000), imply that endurance training might also be effective in enhancing motor neuronal PICs. Thus, in addition to resistance training, endurance training might be a promising tool for use in counteracting the age-related decline in PICs. Potentially arguing against its efficacy, however, is recent cross-sectional data obtained in our laboratory revealing ΔF values of only 2.3 (95% confidence interval = 1.6–3.0) pps in soleus muscle in recreational runners (unpublished observations - Fernandes, G.L., Orssatto, L.B.R., Trajano G.S.), which is similar to data obtained from untrained individuals using the same testing procedures and muscle [e.g. 2.8 (95% confidence interval = 2.4–3.2) pps] (Orssatto, Borg, Blazevich et al., 2021). Still, a well-designed longitudinal intervention investigating the effects of endurance training on estimates of the PIC contribution to motor neurone firing in both young and older adults is warranted with respect to providing robust data in relation to the question.

What is not known about PICs with respect to ageing and exercise

There is compelling evidence for a reduction in the PIC contribution to motor neurone firing during ageing in humans. Resistance training represents a promising tool for addressing this issue because recent research has demonstrated its potential efficacy (Krutki et al., 2017; Orssatto et al., 2023). Despite these encouraging findings, several research questions remain unanswered, highlighting the need for further investigation in the field.

The hypotheses drawn in the present review in relation to the mechanisms underpinning the reductions in PICs with ageing are yet to be explored. This is a big challenge because direct measures of, for example, serotonergic input onto motor neurones are properties of voltage-gated channels are invasive and not feasible yet in humans. Thus, pharmacological or exercise strategies for manipulation of monoamines input onto motor neurones – such as blockade of 5-HT₂ receptors to attenuate ΔF (Goodlich et al., 2023) or varying contraction intensities (Orssatto, Mackay et al., 2021, 2023) and the use of remote contractions to increase ΔF (Orssatto, Fernandes et al., 2022) – could be further explored to understand the role of serotonin on age-related reductions in PICs.

An important limitation in the literature is the lack of data for higher intensity contractions. Stronger contractions recruit higher-threshold motor neurones, which

have characteristics distinct from lower-threshold motor neurones and may be better associated with specific daily living functional activities. Higher-threshold motor neurones are more susceptible to age-related deterioration (Hepple & Rice, 2016) and young-older adult differences in motor unit firing frequencies are greater at higher/maximal contraction intensities (Orssatto, Borg, Pendrith et al., 2022). ΔF s have been compared between older and young adults with contraction intensities up to 20% of maximal capacity (Guo et al., 2023; Hassan et al., 2021; Orssatto, Borg, Blazevich et al., 2021) and the effects of resistance training have been investigated with intensities up to 40% (Orssatto et al., 2023). This limitation is primarily a result of the method employed to estimate PICs. The motor unit decomposition algorithm used with high-definition EMG recordings yields fewer motor units and has limited ability for identifying lower-threshold motor units at higher-intensity contractions, which are crucial for calculating ΔF . Additionally, the slow increase and decrease of force inherent to ramped contractions used in the paired motor unit analysis may induce fatigue when higher intensity contractions are performed, leading to confounding factors in PIC estimations. Therefore, further developments in the technique are necessary to ensure valid estimates of PIC contribution to motor neurone firing at higher contraction intensities.

Currently, there is limited knowledge of the impact of physical inactivity/deconditioning, which is more common in older adults, on PICs, as well as the influence of PICs on the age-related reduction in physical function and their improvement following exercise. The available data suggest moderate-to-strong correlations between changes in ΔF and improvements in strength and functional capacity following resistance training in older adults (Orssatto et al., 2023). However, it remains unclear whether impaired PIC contributions to motor neurone firing could be a determinant process underpinning exacerbated functional loss and strength in sarcopenic or frail individuals (Clark, 2023). A variety of acute and chronic interventions could be explored with the aim of understanding its effects on ΔF values and its translation to enhanced physical function in older populations (Orssatto, Mesquita et al., 2021), including different exercise modalities (e.g. aerobic or different models of resistance training), nutritional (e.g. tryptophan-rich foods or supplements), breathing (e.g. acute intermittent hypoxia) and pharmacological interventions (e.g. selective serotonin reuptake inhibitors or amphetamines).

Technical considerations

The determination of ΔF is contingent on the precise representation of synaptic input to the motor pool by lower threshold control units (Fig. 1). Modulation of

lower threshold motor units that alter the ascending or descending phase of discharge, such as those induced by inhibitory input, has the potential to influence ΔF estimations and introduce uncertainty in hysteresis interpretations. Thus, the use of geometric approaches (e.g. brace height) appears to be an innovative method to be considered in conjunction with ΔF calculations when investigating the effects of ageing and resistance training (Beauchamp et al., 2023). This method quantifies firing non-linearities introduced by PIC amplification during linear tasks to estimate neuromodulatory and inhibitory contributions to individual motor unit firing (Beauchamp et al., 2023). However, this novel measurement has not been employed on aged individuals to date.

The accurate determination of ΔF relies on the presence of common synaptic inputs between each pair of motor units analysed. However, motor neurones from the same muscle do not necessarily receive common synaptic inputs (Hug et al., 2023). Currently, rate-to-rate correlations of the firing frequencies are performed to verify the presence of common input between the test and the control units. However, the triangular nature of the task imposes a mechanical constraint that leads to an increase/decrease in firing frequencies, which may result high correlation coefficients regardless of the presence of common input. Thus, further studies are needed to determine whether (i) the mechanical constraint related to the triangular-shaped contractions generates an estimation of synaptic input to the control unit that could be paired with motor units with distinct synaptic input to produce valid ΔF values or (ii) the development of robust measures of synaptic input commonalities across motor units during triangular-shaped contraction is needed to ensure valid ΔF calculations.

It is worth noting that Ca^{2+} PIC channels are capable of being activated below the threshold for action potential firing (i.e. subthreshold PICs) (Li et al., 2004). However, the ΔF method exclusively estimates the suprathreshold influence of PICs on the firing characteristics of motor units. As such, the ΔF approach cannot provide insight into the operation of subthreshold PICs (Afsharipour et al., 2020).

The ΔF calculation using the paired-motor unit analysis is highly sensitive to slight variations in the testing protocol, such as changes in the rate of torque rise and decline, as well as the inclusion of a sustained isometric contraction phase as a result of spike-frequency adaptation and spike-threshold accommodation. The inclusion of a hold phase can increase ΔF (Vandenberk & Kalmar, 2014), whereas faster rates of torque rise and decline reduce ΔF (Powers & Heckman, 2015). Thus, assessment characteristics should be kept in mind when comparing different studies and interpreting absolute changes in force levels after interventional studies.

Conclusions and future directions

Reduced PIC magnitude is a novel mechanism underpinning the lower motor neuronal firing frequencies observed with ageing. These changes may explain the lower maximal force production ability and consequent impaired motor function in older adults. Age-related impairments within serotonergic and noradrenergic systems and their subsequent input onto motor neurones, as well as impairments in voltage-gated calcium channels and inhibitory input, are candidate mechanisms for explaining the reduction in the PIC contribution to motor neurone firing with ageing; however, these hypotheses remain to be explicitly tested in the future. Furthermore, the understanding of mechanisms underlying the age-related changes in motor neuronal PICs is crucial to the development of effective interventions for maintaining motor function in older adults.

Resistance training induces several neural adaptations in the aged nervous system that explain most of the early increases in muscular strength. Recent animal and human studies have suggested that resistance training increases motor neurone PICs magnitude, leading to increases in motor unit firing frequency, motor function and strength. The reasons for the greater PIC contribution to motor neurone firing are not clear, but potential mechanisms include enhanced monoaminergic drive and voltage-gated calcium channel function, as well as decreases in inhibition. Future studies should investigate the hypothesis that different exercise modalities, such as endurance training, might also enhance motor neuronal PICs. Overall, the current findings suggest that resistance training is a promising intervention to counteract the age-related reductions in PIC contributions to motor neurone firing at the same time as improving physical function in older adults.

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Additional information

Competing interests

The authors declare that they have no competing interests.

Author contributions

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