DO MOTONEURONS SLOW WITH AGING? A SYSTEMATIC REVIEW AND META-ANALYSIS WITH META-REGRESSION

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ABSTRACT

Nervous system maladaptation is linked to the loss of muscle force production and motor control with aging. However, the mechanisms specifically underpinning these muscle functional limitations remain unclear. Motoneuron discharge rates are a critical determinant of force production and strongly impact motor control; thus, lower discharge rates could underpin force and physical function losses during aging. The present meta-analysis with meta-regression summarises the findings of studies comparing motoneuron discharge rates between young and older adults and examines whether a muscle's functional role and anatomical location influences discharge rates across contraction intensities during aging. Meta-analysis revealed lower discharge rates in older compared to young adults in lower body flexor (standardised mean difference, SMD=-0.86; 95%CI: -1.20, -0.51; $p<0.001$) but not extensor (SMD=-0.18; 95%CI: -0.50, 0.15; $p=0.29$) muscles or upper body muscles (SMD=-0.79; 95%CI: -1.75, 0.18; $p=0.11$). Meta-regression revealed that the differences in discharge rate between young and older adults increase with contraction intensity in upper body muscles ($\beta=-0.033$, $p=0.004$). These findings suggest that motor function loss with aging might be partly explained by reduced motoneuron discharge rates; however, this decrease varies according to a muscle's anatomical location, functional role, and contraction intensity.

1. INTRODUCTION

Aging is accompanied by a notable reduction in the ability to produce muscular force and power as well as a decline in the maximal rate of force development, which influences our capacity to perform physical activities of daily living (Bergland and Strand, 2019; Orssatto et al., 2020; Suetta et al., 2019; Tomás et al., 2018). These reductions are clearly observed after 50-60 years of age and the force, power and functional capacity losses accelerate during the subsequent decades of life (Larsson et al., 2019; Suetta et al., 2019; Vandervoort, 2002). Changes within the neuromuscular system have been investigated in order to understand the mechanisms underpinning the differences in force production across the lifespan (Hunter et al., 2016; Larsson et al., 2019; Manini et al., 2013; Orssatto et al., 2018). In addition to alterations within the muscles themselves, the role of neural factors needs to be clearly defined, given that muscle output will be limited by the neural input arriving from the motoneurons.

Both the number of recruited motor units and their discharge rates can be readily modulated by the central nervous system in order to regulate muscle forces; higher forces are achieved by an increase in the number of active motor units and/or their discharge rates (Enoka and Duchateau, 2017). The relative importance of motor unit recruitment versus discharge rate to the force rise differs significantly between muscles (De Luca and Kline, 2012) and important changes have been observed at the motor unit level during aging (Manini et al., 2013; Orssatto et al., 2018). Over at least the last four decades, researchers have investigated the effects of human aging on motor unit discharge rates during sustained isometric contractions (Kamen et al., 1995; Kirk et al., 2016; Mota et al., 2020; Nelson et al., 1983; Vaillancourt et al., 2003). However, inconsistent results have been observed when comparing young and older individuals, with some studies identifying lower (Christie and Kamen, 2010; Connelly et al., 1999; Gary Kamen and Knight, 2004; Kirk et al., 2019, 2018) but others similar mean discharge rates for a given proportional level of force during sustained isometric contractions (Christie and Kamen, 2009; Kallio et al., 2010; Kamen and Roy, 2000; Kirk et al., 2016). This inconsistency may be partly explained by the wide range of methods used across studies, with variations in the (i) muscles studied, often with them having distinct anatomical functions and locations (e.g., flexors/extensors and upper/lower body); and (ii) contraction intensities produced (2.5 to 100% of maximal voluntary force). Because of these differences, it has been difficult to draw broad conclusions based on data from any single study. In this case, a systematic review and analysis that pools the available data presented across studies could provide evidence that is more robust in relation to the effect of aging on motor unit discharge rates.

Given the above, the aim of the present systematic review and meta-analysis with meta-regression is to identify and summarize the findings, and then estimate the effects, of studies comparing motor unit discharge rates between young and older participants during maximal and submaximal isometric sustained contractions. Thereafter, we discuss the potential influence of muscle anatomical location, functional role, and contraction intensity on differences in motor unit discharge rates between younger and older individuals.

2. METHODS

2.1. Systematic search strategy

A systematic literature search was conducted in three electronic databases (i.e., PubMed, Web of Sciences, and Scopus) in January 2020 and repeated in November 2020 (second search limited to articles published in 2020). The chosen search terms related to aging (e.g., age, elderly, older, and aging), motor units, and discharge rate (e.g., discharge rate, firing frequency, and inter-spike interval). The reference lists of the selected studies were screened for additional studies. The search procedures are reported in the Preferred Reporting Items for

Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (Liberati et al., 2009; Moher et al., 2009) (Figure 1). The systematic search strategy was designed by LBRO and GST and conducted independently by LBRO and LP.

2.2.Eligibility criteria

Studies were selected according to the following inclusion criteria: i) compared groups based on age (young = 18–40 years and elderly ≥60 years); ii) adopted electromyographic methods allowing the identification of motor unit discharge rate; iii) discharge rate was measured during a sustained isometric contraction; iv) force level chosen for testing was based on a percentage of the each participant's maximal voluntary force; and v) peer-reviewed and published in English. Studies were excluded if they included participants with neurological (e.g., Parkinson disease, Alzheimer's) or musculoskeletal disorders (e.g., osteoarthritis, limb injury), involved explosive or dynamic contractions, or if data analyses or the test task were not clearly reported.

2.3. Data extraction

Data extracted from the selected studies included the country of the corresponding author, participant sample size, participants' characteristics and ages, muscles tested, relative force level reached during testing, and mean discharge rates for both young and older groups. For studies reporting chronic or acute intervention results (e.g., exercise training, fatiguing protocol, or visual gain) the baseline or control group/condition data were extracted. Data were converted to discharge rates for studies reporting inter-spike intervals. When data were reported in graphs, WebPlot Digitizer software (version 4.1) was used to extract the data. LBRO and LP conducted all data extraction independently before comparing results; mean variation between researchers was <1%. The mean values from data extracted by LBRO and LP were used for the analyses.

2.4. Data analyses

Our primary interest was to investigate whether differences in discharge rates exist between younger and older adults, with a specific focus on differences in lower body flexor muscles, lower body extensor muscles, and upper body muscles. A second interest was to examine the effect of contraction intensity on differences in motor unit discharge rates between younger and older adults.

Estimates from studies were combined within the meta-analysis using a random-effects model and presented as forest plots. The Hartung-Knapp-Sidik-Jonkman method was used as the estimator for the variance of the distribution of the true effect sizes, τ^2 (Inthout et al., 2014). This estimator for τ^2 method generally produces more conservative results (i.e., wider confidence intervals), particularly when the number of studies is small and between-study heterogeneity is large (Inthout et al., 2014). The standardised mean difference (SMD; Hedges' *g*) in motor unit discharge rates between younger and older adults was used because it was not always clear whether discharge rates were reported per motor unit or per participant.

Meta-regressions were used to determine the effect of contraction intensity on the SMD in discharge rates between younger and older adults. Separate models were run for lower body flexor muscles, lower body extensor muscles and upper body muscles; insufficient data existed to compare flexor and extensor muscles in the upper body. When studies examined differences across a range of contraction intensities, the effects were pooled for the meta-analysis. However, because pooled effects were not representative of any specific contraction intensity, non-pooled effects were used in the meta-regressions.

The I^2 statistic was used to examine between-study heterogeneity, with higher values denoting greater heterogeneity (Higgins and Thompson, 2002). Where significant between-study heterogeneity was observed, a Graphic Display of Heterogeneity plot was used to explore the patterns of heterogeneity. Sensitivity analysis was performed to determine the robustness of meta-estimates by comparing estimates before and after removing the single studies with the largest and smallest weights, respectively. Publication bias was evaluated using a funnel plot (Egger et al., 1997) and *p*-curve analysis (Simonsohn et al., 2014). Funnel plot asymmetry was examined using Egger's test of the intercept (Egger et al., 1997).

All analyses were conducted in R (version 4.0.3) using the RStudio environment (version 1.1.447) and the *meta* (Balduzzi et al., 2019), *metafor* (Viechtbauer, 2010) and *dmetar* (Harrer et al., 2019) packages. The α for all tests was set at 5%. The data and R code that support the findings in this article can be accessed at https://github.com/orssatto/SRMA_MU.

3. RESULTS

3.1. Systematic search

The systematic search conducted in January 2020 retrieved 1056 studies and after duplicates removed, 945 study titles and abstracts were read for eligibility. After removing 890 studies, 55 studies were read in full and 30 were excluded according to the set criteria, resulting in 25 studies being included in the review. After repeating the search in November 2020, 73 studies were identified, 66 after duplicates removed, and no additional manuscript was included in the review. Figure 1 shows the PRISMA flow diagram for all steps of the systematic search.

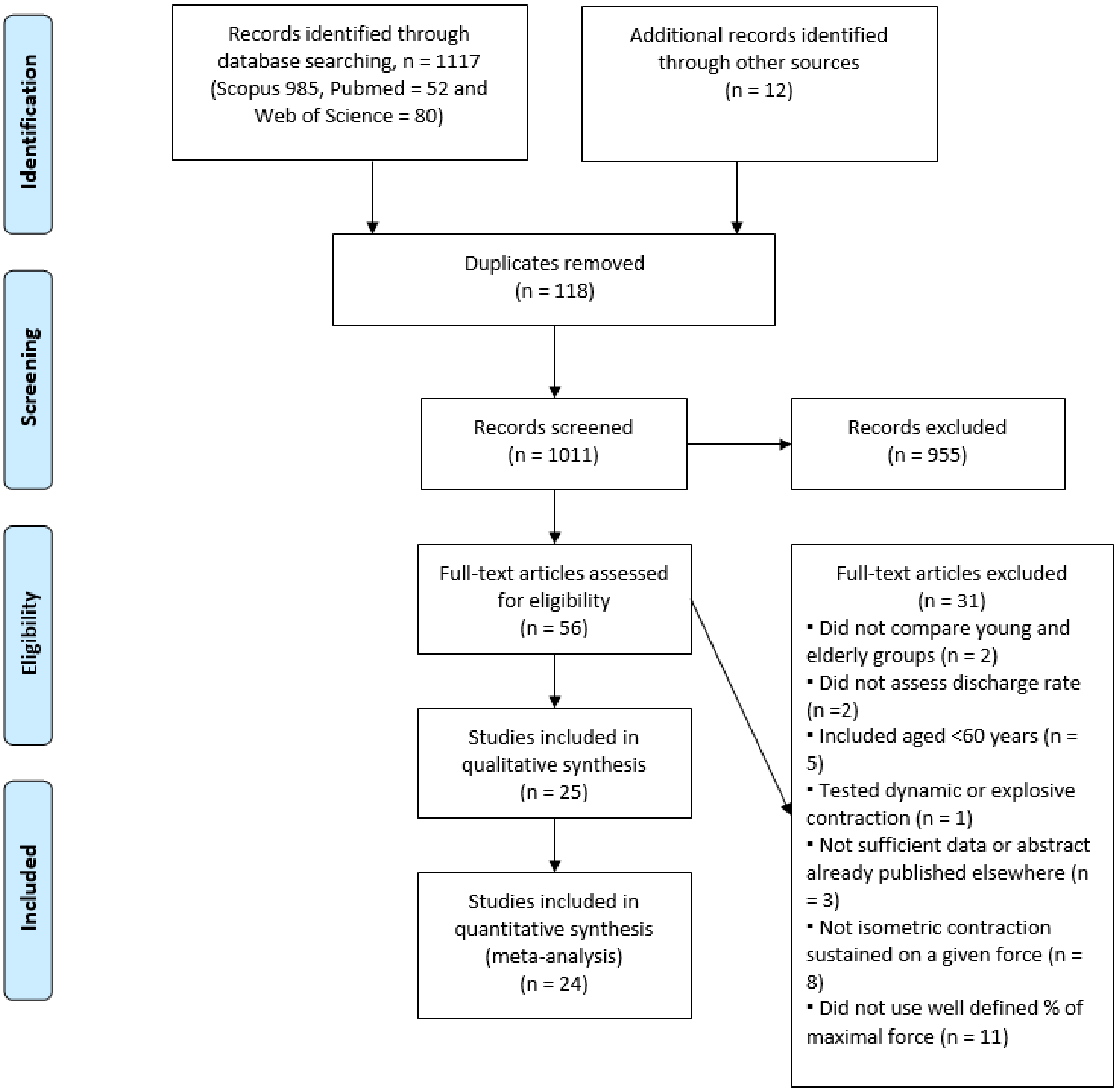

Figure 1. PRISMA flow diagram for the systematic search.

3.2.Study characteristics

Of the 25 included studies, 16 were conducted in the United States of America, 7 in Canada, 1 in Finland, and 1 in the United Kingdom. Studies tested a total of 303 young and 319 older participants. Different muscles were tested, including upper and lower body, flexors and extensors, and hand muscles. Most studies used intramuscular electromyography, except for four studies that used multichannel surface electromyography (5-pin electrodes, n = 2; and

32- or 64-channel electrodes, n = 2). The contraction intensities ranged from 2.5% to 100% of the participants' maximal voluntary contraction forces.

Table 1 near here

3.3. Meta-estimates

Twenty-four studies were used for the meta-analysis, six of which examined lower body extensor muscles, seven examined lower body flexor muscles, and 11 examined upper body muscles. Kamen and Knight (2004) was not included in the meta-analysis, because we were unable to retrieve all necessary data. The pooled effects of the 24 studies are shown in Figure 2. There was evidence of differences in motor unit discharge rates between younger and older adults in lower body flexor muscles (SMD = -0.86, 95% CI: -1.20 to -0.51, $p < 0.001$), but not lower body extensor muscles (SMD = -0.18, 95% CI: -0.50 to 0.15, $p = 0.29$) or upper body muscles (SMD = -0.79, 95% CI: -1.75 to 0.18, $p = 0.11$).

There was significant between-study heterogeneity for investigations of upper body muscles (I^2 = 74%, 95% CI: 52% to 86%, $p < 0.001$). The Graphic Display of Heterogeneity plot (Supplementary material 1) indicated that this was largely attributed to three studies (Dalton et al., 2010; Kirk et al., 2019; Vaillancourt et al., 2003), and a marked reduction in heterogeneity (I^2 = 11%, 95% CI: 0% to 71%, $p = .34$) and decrease in the pooled mean effect (SMD = -0.35, 95% CI: -0.71 to 0.01, $p = .056$) was found when these three studies were removed.

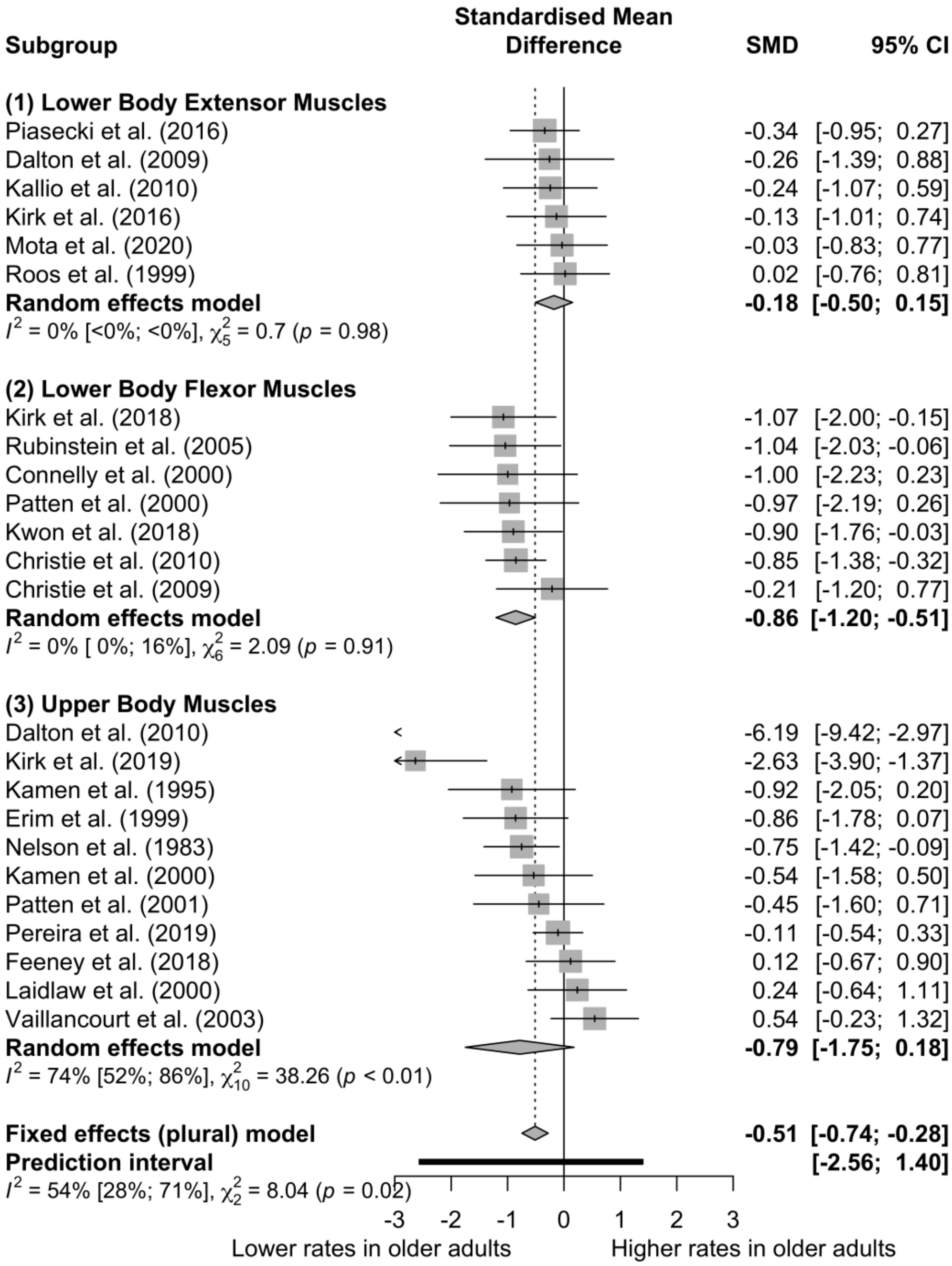

Figure 2. Estimates of differences in motor unit discharge rates between younger and older adults in lower body extensor muscles, lower body flexor muscles, and upper body muscles.

3.4. Meta-regression

Contraction intensity was statistically associated with effect size differences in upper body muscles (β = -0.033, F = 8.40, p = 0.004; Figure 3C), with contraction intensity explaining 22% of the variability in the effect size data (R^2 = 21.9%). Contraction intensity was not significantly associated with effect size differences in the lower body extensor (β = 0.001, F = 0.04, p = .84, R^2 = 00.0%; Figure 3A) or flexor (β = -0.006, F = 1.96, p = 0.16, R^2 = 11.9%; Figure 3B) models. Notably, these associations remained unchanged when a single meta-regression model was fitted, with *contraction intensity*, *subgroup* and *contraction intensity* by *subgroup* included as predictor variables.

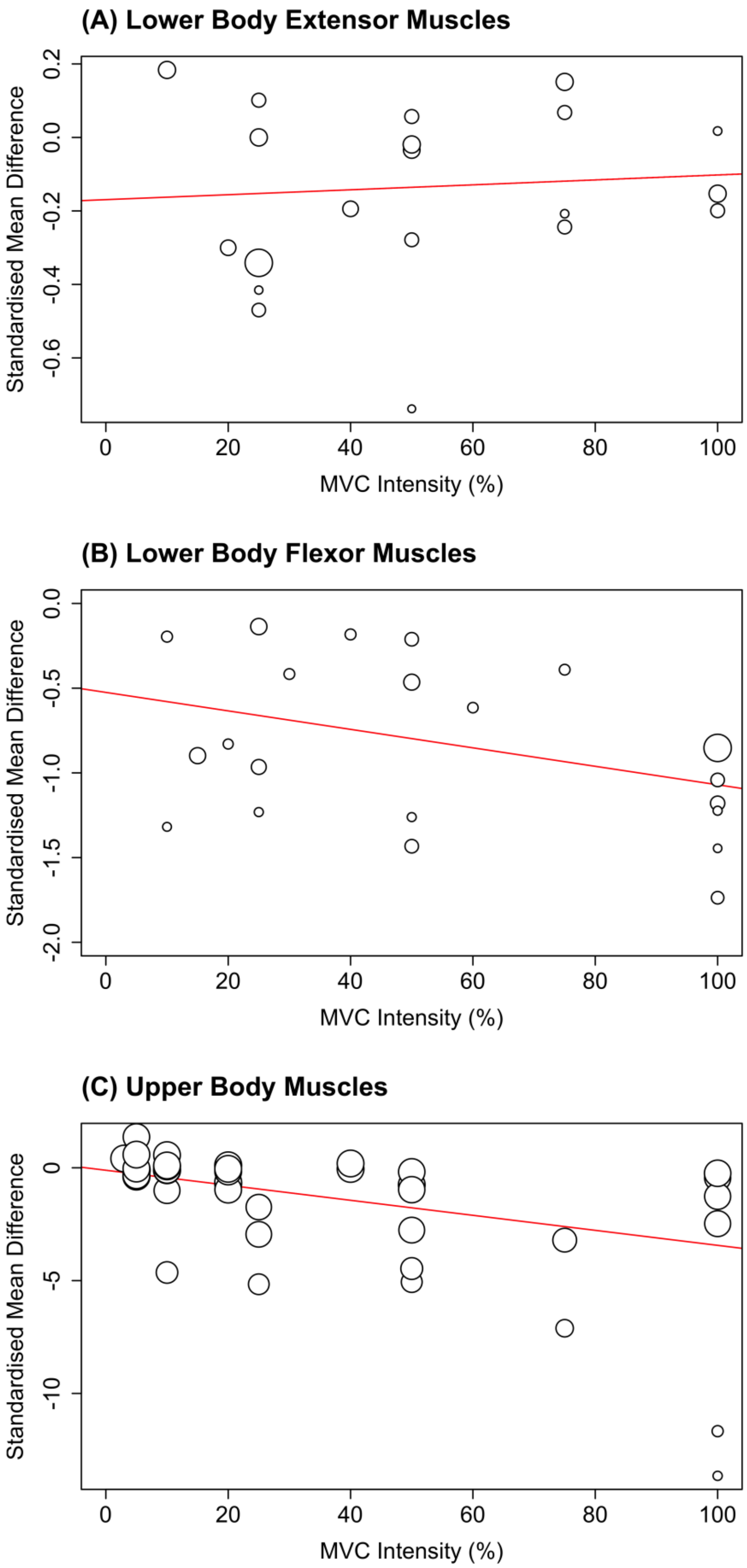
(A) Lower Body Extensor Muscles
Standardised Mean Difference
0.2
0.0
-0.2
-0.4
-0.6
0
20
40
60
80
100
MVC Intensity (%)
(B) Lower Body Flexor Muscles
Standardised Mean Difference
0.0
-0.5
-1.0
-1.5
-2.0
0
20
40
60
80
100
MVC Intensity (%)
(C) Upper Body Muscles
Standardised Mean Difference
0
-5
-10
0
20
40
60
80
100
MVC Intensity (%)

Figure 3. Bubble plots with fitted meta-regression lines indicating the effect of contraction intensity on the standardised mean difference in motor unit discharge rates between younger and older adults in lower body extensor (A), lower body flexor (B), and upper body (C) muscles. The size of each point is inversely proportional to the variance of the estimated difference. Negative standardised mean differences indicate lower discharge rates in older adults.

3.5. Sensitivity analysis

Table 2 shows the results from the sensitivity analysis. The pooled SMD changed only marginally after removing the study with the largest weight, except for the upper body muscles subgroup in which the removal of Dalton et al., (2010) resulted in a marked SMD change from -0.79 (95% CI: -1.75 to 0.18) to -0.46 (95% CI: -1.00 to 0.08). Removing the study with the smallest weight resulted in only marginal SMD change for lower body flexor and extensor muscles. In contrast, removing the study by Vaillancourt et al. (2003) resulted in a marked SMD change for upper body muscles, from -0.79 (95% CI: -1.75 to 0.18) to -0.93 (95% CI: -1.96 to 0.09).

Table 2. Results of the sensitivity analysis.

Subgroups	All studies included	Study with the largest weight excluded	Study with the smallest weight excluded
	Pooled standardised mean difference [95% CI]		
Lower body extensor muscles	-0.18 [-0.50, 0.15]	-0.11 [-0.50, 0.28]	-0.22 [-0.58, 0.14]
Lower body flexor muscles	-0.86 [-1.20, -0.51]	-0.82 [-1.20, -0.45]	-0.93 [-1.28, -0.59]
Upper body muscles	-0.79 [-1.75, 0.18]	-0.46 [-1.00, 0.08]	-0.93 [-1.96, 0.09]

Note: CI = Confidence interval

3.6. Publication bias

Supplement material 2 shows the funnel plot. Egger's test indicated the presence of asymmetry in the funnel plot (*intercept* = -2.23, 95% CI: -3.88 to -0.59; t = -2.66; p = .014), which may have been caused by publication bias, when studies with small samples and small effect sizes are missing. However, the p-curve was right-skewed (Supplement 3), indicating that there was a 'true' effect underlying the findings and that the results were most likely not the result of publication bias alone.

4. DISCUSSION

4.1. Main findings

The present meta-analytic review interrogated the current literature to determine the effects of aging on motor unit discharge rates. We summarised the findings of studies comparing motor unit discharge rates between young and older adult participants during sustained maximal and submaximal isometric contractions. We also attempted to determine the influence of contraction intensity and both muscle anatomical location and functional role on motor unit discharge rates during aging. The main findings were that the reductions in motor unit discharge rates at a given relative force level might depend on the muscle anatomical location, functional role, and contraction intensity. Older adults produced lower discharge rates than young adults in lower body flexor muscles but not in lower body extensors or upper body muscles. However, high between-study heterogeneity was observed for upper body muscles. Also, an influence of contraction intensity on the difference between younger and older adults was also observed for upper body muscles. Likewise, discharge rates at MVC were also lower in older adults. These results show why inconsistent results have been observed in the extant literature as to the effects of aging on motor unit discharge rates, and they thus contribute to our understanding of the effects of aging on neural control during sustained isometric submaximal and maximal contractions.

4.2. The effect of muscle anatomical location and function on discharge rate differences between young and older adults

Age-dependent differences in discharge rates are not readily apparent in studies in which lower limb extensor or upper limb muscles were studied but are clear in studies of lower limb flexor muscles. The effect of aging on discharge rates therefore appears to be specific to a muscle's anatomical location (upper vs. lower body) and function (extensor vs. flexor). Differences between muscles of different anatomical location might speculatively be explained by the characteristics of the descending tracts that innervate these muscle groups (Taylor et al., 2000). For example, previous studies in the ventral spinal cord of the decerebrate cat and neonatal rat as well as estimations of motoneuron excitability in humans have shown a greater excitability of extensor than flexor motoneurons (Cotel et al., 2009; Hounsgaard et al., 1988; Wilson et al., 2015). Lower body extensors commonly serve an anti-gravity role, meaning that they are active for longer periods and produce greater cumulative force than flexor muscles during activities of daily living, including during upright standing and locomotor propulsion (e.g., walking) (Masani et al., 2013; Soames and Atha, 1981). These functions may be associated with a lesser risk of discharge rate loss with aging. Additional evidence for this assertion is provided by the findings that, while disuse can aggravate the deleterious effects of aging on the nervous system, master-level (i.e. older adult) athletes show a substantial preservation of neural function (Aagaard et al., 2010; Hvid et al., 2018; McGregor et al., 2011; Unhjem et al., 2016).

4.3. The role of contraction intensity on discharge rate differences between young and older adults

We also examined whether stronger contraction levels might exacerbate age-dependent differences in motor unit discharge rates through use of meta-regression analyses. The results showed a statistical effect of contraction intensity on discharge rate differences only for studies investigating upper body muscles (Figure 3C). However, it should be pointed out that there was a notable effect of intensity on the difference in discharge rates in lower body flexor muscles (β = -0.006, p = 0.16; Figure 3B), despite statistical significance not being reached; that is, there was a mean reduction in discharge rates with aging, with the propensity for greater reduction at higher contraction intensities. For context, at a contraction intensity of 50% MVC, intensity alone accounted for (SMD) -0.3 of the difference between younger and older adults. Also, Figure 3 shows a clear lower discharge rate for older adults during maximal contractions for upper body and lower body flexors. Nonetheless, no contraction intensity influence was observed in lower body extensor muscles.

The reduction of discharge rates during maximal contractions is likely a factor resulting in the reduced and more variable muscle voluntary activation level observed in older adults (Jakobi and Rice, 2002; Rozand et al., 2020). Discharge rate declines may also underpin compression of the range of discharge rates observed in older adults (Barry et al., 2007). The reduction in discharge rates, particularly at high contraction levels, might reflect both functional and structural changes within the nervous system. Hypothetically, mechanisms contributing to a potential motoneuron discharge rate reduction may include i) the motoneuron's intrinsic characteristics, which affects their recruitment threshold (Heckman and Enoka, 2012; Piotrkiewicz and Türker, 2017); and ii) the effect of neuromodulation on motoneuron excitability (Heckman et al., 2009; Johnson and Heckman, 2014).

At the motoneuron level, several age-related structural and functional changes may explain the greater reduction in motoneuron discharge rate in higher-force contractions. Central to this is that motoneurons are affected by axonal demyelination, atrophy and degeneration during aging (Jang and Remmen, 2011; McKinnon et al., 2015; Misgeld, 2011; Selman et al., 2012). This motoneuron deterioration can trigger muscle fibre denervation, resulting in some fibres being unable to contribute to force production (Aare et al., 2016). Whilst a compensatory mechanism allows low-threshold motoneurons to reinnervate some nearby denervated type II muscle fibres (Hepple and Rice, 2015), it does not prevent the reduction in motor unit discharge rate since the lower-threshold reinnervating motoneuron will exhibit slower discharge rates (Deschenes, 2011; Piasecki et al., 2016). As a result, older adults have fewer (McNeil et al., 2005; Mittal and Logmani, 1987; Tomlinson and Irving, 1977) but larger MUs, a greater proportion of which are innervated by low-threshold motoneurons (Dalton et al., 2008; Lexell and Taylor, 1991). Although debate exists (Piotrkiewicz and Türker, 2017), motor units innervated by higher recruitment-threshold motoneurons should discharge at higher rates during contractions close to maximal force. However, at lower contraction intensities, motor units innervated by lower threshold motoneurons typically discharge at higher rates than those innervated by higher threshold neurons, which typically start to discharge at higher rates as force level increases (Hu et al., 2014; Oya et al., 2009). As older adults typically possess fewer higher threshold motoneuron, this might explain the lower rate relative to younger adults at higher intensities contractions in lower body flexor and upper body muscles.

Motoneuron discharge rates are also influenced by neuromodulatory inputs (i.e., serotonin and noradrenalin) from the monoaminergic system, which affects motoneuron intrinsic excitability. Monoamines exert strong facilitation onto motoneurons by triggering persistent inward calcium and sodium currents, and reducing recruitment thresholds by increased conductance and reduced amplitude and duration of the afterhyperpolarisation when

PICs are strongly active (Heckman et al., 2008; Lee and Heckman, 1999, 1998). Reduced serotonin concentrations (Ko et al., 1997), axonal degeneration in serotonergic neurons (Johnson et al., 1993), and a decline in the activity of noradrenergic neurons emanating from the locus coeruleus (the primary source of noradrenalin-releasing axons in the spinal cord) (Olpe and Steinmann, 1982; Vijayashankar and Brody, 1979) suggest that aging negatively affects the monoaminergic system. Therefore, older adults should have an impaired ability to facilitate motoneuron excitability, although experiments exploring these mechanisms are yet to be performed in humans. Also, some evidence indicates that motoneurons of older adults exhibit greater afterhyperpolarisation duration (Piotrkiewicz et al., 2007), which indicate a reduced net excitability. Taken together, the smaller number and proportion of higher-threshold motoneurons as well as an impaired neuromodulation that could limit motoneuron excitability may collectively limit motoneuron discharge rates during high-intensity, more than low-intensity, contractions.

4.4. Limitations

Despite the relevance of the current findings, some limitations should be mentioned. First, our search only identified studies conducted in developed countries (i.e., USA, Canada, Finland, and United Kingdom). It is unclear if, for example, whether the potentially longer life expectancy and better physical health in individuals from developed countries might influence the research findings. Also, studies investigating sex-related effects of aging on motor unit discharge rates are lacking. Only one study (Pereira et al., 2019) compared older and younger men and women, whilst other studies only tested men, combined male and female data, or did not report the participants' sex (Table 1). Thus, it was not possible to explore potential sex-related differences on motor unit discharge rate reductions during aging; future studies are clearly warranted to address this issue. Another important limitation of the literature is the small number of studies investigating upper body flexor (Dalton et al., 2010; Pereira et al., 2019) and extensor muscles (Pereira et al., 2019), which did not allow meta-analysis to be used to compare these muscle groups. In the upper body, most studies tested muscles located in the hand or shoulder girdle (trapezius). Also, only studies adopting sustained isometric contractions and in which motor unit discharge rates were measured during the contraction plateau were included in our systematic search. This methodological restriction allowed a better control for between-study comparisons because motor unit discharge behaviour is contraction mode dependent (i.e., isometric vs. concentric vs. eccentric) and varies with movement velocity (i.e., fast or slow) and the phase of isometric force production (i.e., torque rise, plateau or decline). However, this inclusion criterion could mask some potential age-related differences that may occur in other contractions or movement tasks. For example, evidence exists that motor unit discharge rates during explosive contractions may be more sensitive to aging (Klass et al., 2008); however, more studies are required before clear conclusions can be drawn. Therefore, our findings may only be reflective of those during isometric contractions.

5. CONCLUSIONS

The present systematic review identified 25 studies reporting mixed results regarding the differences in motor unit discharge rates during sustained isometric contractions between young and older adults. Several patterns regarding age-related reductions in discharge rate were identified. In upper body muscles, no significant differences were observed between young and older adults. Lower body extensor muscles discharge rates also seem to be maintained in older adults, however lower body flexor discharge rates were markedly reduced, irrespective of contraction intensity. These data suggest that discharge rates are only consistently reduced in some muscles, whilst discharge rate is preserved in others. Identifying the factors underpinning the retention of discharge rate may be important to develop methods to retain discharge rate in other muscles, such as the lower body flexor muscles. Further, a greater difference in discharge rates for young and older adults has been observed for higher contraction intensities in upper body muscles. Interpretation for upper body muscles data should be made with some caution because between-study heterogeneity was high; particularly in higher intensity contractions, and differences could potentially range from negligible to large.

It is important to consider that these findings may only be reflective of motor unit behaviour during isometric contractions. There was also considerable methodological heterogeneity among studies regarding the muscles examined, contraction intensities used, discharge rate measurement techniques, and the age-range of participants. These aspects of study design require careful consideration by future investigations.

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Table 1. Studies characteristics

Authors	Country	Young participants		Elderly participants		Characteristics	Tested muscles	EMG methods
		Age (years)	Sample (sex)	Age (years)	Sample (sex)			
Christie and Kamen, 2009	USA	23.9 ± 4.1	8 (F=4; M=4)	75.6 ± 6.7	8 (F=3; M=5)	Inactive to moderately active (30 min of exercise three times per week or less	Tibialis anterior	Intramuscular
Christie and Kamen, 2010	USA	21.9 ± 3.1	30 (F=15; M=15)	72.9 ± 4.6	30 (F=15; M=15)	Relatively sedentary (structured physical activity less than 3 days/week).	Tibialis anterior	Intramuscular
Connelly et al., 1999	Canada	20.8 ± 0.8	6 (M)	82.0 ± 1.7	6 (M)	Recreationally active with a mean of 6.7h/week (old) and 7.6 h/week (young)	Tibialis anterior	Intramuscular
Dalton et al., 2009	Canada	23.5 ± 2.9	6 (M)	75.3 ± 4.1	6 (M)	Recreationally active. Young: University students. Old: in a program to maintain muscular endurance, cardiovascular fitness, and flexibility.	Soleus	Intramuscular
Dalton et al., 2010	Canada	24 ± 2.4	6 (M)	83 ± 9.8	6 (M)	Healthy and recreationally active.	Triceps brachii and biceps brachii	Intramuscular
Erim et al., 1999	USA	30.2 ± 5.7	10 (NR)	76.9 ± 6.6	10 (NR)	No activity level or hand usage was recorded.	First dorsal interosseous	Intramuscular
Feeney et al., 2018	USA	25 ± 4	13 (F=8; M=5)	78 ± 5	12 (F=5; M=7)	No history of neurological disease or injury to the upper extremity	Extensor digitorum	Surface 32-channels electrode
Kallio et al., 2010	Finland	27.3 ± 3	10 (M)	70.4 ± 5	13 (M)	Physically active males without any history of neuromuscular or vascular disease.	Soleus	Intramuscular
Kamen et al., 1995	USA	R(21 – 33)	7 (NR)	R(67 – 85)	7 (NR)	Free of musculoskeletal and neuromuscular complaints. Varied in	First dorsal interosseous	Intramuscular

						fitness levels, to give a representative sample of elderly adults.		
Kamen and Roy, 2000	USA	27.7 ± 4.3	7 (NR)	74.9 ± 7.1	8 (NR)	Free of any known neuromuscular, musculoskeletal or cardiopulmonary disorders.	First dorsal interosseous	Intramuscular
Kamen and Knight, 2004	USA	21 (R 18 - 29)	8 (NR)	77 (R 67 – 81)	7 (NR)	None of these persons had resistance training experience within the previous year.	Vastus lateralis	Intramuscular
Kirk et al., 2016	Canada	27 ± 3	10 (M)	81 ± 4	10 (M)	Free from any known neuromuscular, respiratory, cardiovascular and metabolic illness and none were systematically trained or sedentary.	Gastrocnemius	Intramuscular
Kirk et al., 2018	Canada	26 ± 4	11 (M)	80 ± 5	10 (M)	Involved in recreational exercise programs three times a week.	Biceps femoris, semitendinosus and semimembranosus	Intramuscular
Kirk et al., 2019	Canada	R(22 – 33)	10 (M)	R(77 – 88)	10 (M)	Young participants were normally active University students. The older participants were independently living and participated three times per week in an organized fitness and light exercise program	Superior trapezius	Intramuscular
Kwon and Christou, 2018	USA	22.6 ± 4.1	11 (F=6; M=5)	74.1 ± 5.7	12 (F=5; M=7)	Healthy without any neurological impairment and were moderately active.	Tibialis anterior	Surface 5-pins electrode
Laidlaw et al., 2000	USA	26.6 ± 1.6	8 (F=4; M=4)	73.4 ± 6.1	14 (F=8; M=6)	No known neuromuscular disorders and their vision corrected to normal levels.	First dorsal interosseous	Intramuscular
Mota et al., 2020	USA	25 ± 3	12 (M)	75 ± 8	12 (M)	During the 6 months prior to study participation, enrolled participants refrained from lower body resistance	Vastus lateralis	Surface 5-pins electrode

						training (< three times monthly) or other structured exercise (e.g., jogging) more than 30 min per day, three times per week		
Nelson et al., 1983	USA	29.6 ± 4.2	13 (NR)	65.5 ± 2.2	13 (NR)	No current or history of peripheral nerve dysfunction, no current usage of medication known to affect neuronal conduction, and no indication of muscle weakness	Abductor digiti minimi	Intramuscular
				74.8 ± 2.9	9 (NR)			
				83.5 ± 2.8	10 (NR)			
Patten and Kamen, 2000	USA	19.2 ± 1.6	6 (F=3; M=3)	70.3 ± 3.9	6 (F=2; M=4)	Regular participation in vigorous physical activity since at least the age of 40 years. Young and older adult subjects were matched for current participation in physical activity	Tibialis Anterior	Intramuscular
Patten et al., 2001	USA	23.2 ± 3.5	6 (F=3; M=3)	75.8 ± 7.4	6 (F=3; M=3)	Mean weekly time spent participating in physical activity was similar between young (128 min) and older (138 min) adult groups.	Abductor digiti minimi	Intramuscular
Pereira et al., 2019	USA	21.9 ± 2.8*	49 (F=25; M=24)	67.7 ± 5.8*	36 (F=19; M=17)	No statistical differences for physical activity level between young and elderly participants.	Biceps Brachii	Surface 64-channels electrode
Piasecki et al., 2016	United Kingdom	25.3 ± 4.8	22 (M)	71.4 (6.2)	20 (M)	Habitually physically active (not sedentary or participating in competitive sport at regional level or above).	Vastus lateralis	Intramuscular
Roos et al., 1999	Canada	26.2 ± 4.1	13 (M)	80 ± 5.3	12 (M)	Moderately active	Vastus medialis	Intramuscular
Rubinstein and Kamen, 2005	USA	19.2 (R 18-30)	34 (W)	73.1 (R >69)	12 (W)	Engaged in moderate levels of daily physical activity (3–5 days/week).	Tibialis Anterior	Intramuscular
	USA	22 ± 1	10	67 ± 2	10		First dorsal interosseous	Intramuscular

Vaillancourt et al., 2003			(F=5; M=5)		(F=5; M=5)	The subjects were naive to the purpose of the experiment and none had a history of a neurological disorder		
				82 ± 5	10 (F=5; M=5)			

R = range; EMG, electromyography; NR, not reported; M, male; F, female; *pooled mean ± standard deviation from male and female groups.