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Age-related Deficits in Voluntary Activation: A Systematic Review and Meta-analysis

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Abstract

Whether there are age-related differences in neural drive during maximal effort contractions is not clear. This review determined the effect of age on voluntary activation during maximal voluntary

isometric contractions. The literature was systematically reviewed for studies reporting voluntary activation quantified with the interpolated twitch technique (ITT) or central activation ratio (CAR) during isometric contractions in young (18–35 yr) and old adults (>60 yr; mean, ≥65 yr). Of the 2697 articles identified, 54 were eligible for inclusion in the meta-analysis. Voluntary activation was assessed with electrical stimulation and transcranial magnetic stimulation on five different muscle groups. Random-effects meta-analysis revealed lower activation in old compared with young adults (d = −0.45; 95% confidence interval, −0.62 to −0.29; P < 0.001), with moderate heterogeneity (52.4%). To uncover the sources of heterogeneity, subgroup analyses were conducted for muscle group, calculation method (ITT or CAR), and stimulation type (electrical stimulation or transcranial magnetic stimulation) and number (single, paired, or train stimulations). The age-related reduction in voluntary activation occurred for all muscle groups investigated except the ankle dorsiflexors. Both ITT and CAR demonstrated an age-related reduction in voluntary activation of the elbow flexors, knee extensors, and plantar flexors. ITT performed with paired and train stimulations showed lower activation for old than young adults, with no age difference for the single electrical stimulation. Together, the meta-analysis revealed that healthy older adults have a reduced capacity to activate some upper and lower limb muscles during maximal voluntary isometric contractions; however, the effect was modest and best assessed with at least paired stimulations to detect the difference.

The maximal isometric strength and power of limb muscles progressively decrease with advancing age due, in large part, to the age-related reductions in muscle mass ([1,2]), particularly the atrophy of muscle fibers expressing the fast myosin heavy-chain isoform ([3–5]). Inadequate voluntary activation of the available muscle potentially contributes to age-related losses in strength and power, although how important this contribution is for healthy old adults is not clear. Aging is accompanied by multiple impairments within the central nervous system including the motor cortex, spinal cord, motoneuron, and neuromuscular junction ([1,6,7]) that may contribute to a decreased ability to voluntarily activate the muscle with age. For example, discharge rates of motor units are typically lower during maximal and submaximal isometric contractions in upper and lower limb muscles in old compared with young adults ([8–13]) and can be associated with age-related deficits in voluntary activation in some muscles ([12]). These age-related impairments may predispose old adults to deficits in the ability to voluntarily activate limb muscles during maximal contractions.

Voluntary activation during maximal efforts is commonly assessed using the interpolated twitch technique (ITT) ([14]) in both young and old men and women ([15–18]). Typically, electrical stimulation (ES) is delivered to the motor nerve during a maximal voluntary isometric contraction (MVC) ([19]). Any extra force elicited by the stimulation indicates inadequate neural drive and submaximal activation of the muscle. To quantify the level of voluntary activation with the ITT, the extra force evoked, typically with a single or paired stimuli during the MVC, can be expressed relative to the maximal force of a control stimuli evoked at rest ([19]). An alternate measure of voluntary activation, known as the central activation ratio (CAR), involves expressing the force evoked from a train of stimuli to the MVC force ([20]). Although ES over the motor nerve has been primarily used to quantify voluntary activation, the primary motor cortex can be stimulated with transcranial magnetic stimulation (TMS) to determine potential deficits in voluntary activation at motoneuronal or cortical levels ([21,22]).

The findings on whether old adults exhibit reductions in voluntary activation compared with young adults are equivocal. Some studies reported a reduced activation in old compared with young adults ([23–26]), whereas others did not observe an age-related difference ([17,18,27–29]). In a narrative literature review, Klass et al. ([30]) highlighted the heterogeneity of results and suggested that the age-related deficit in voluntary activation was modest during performance of an MVC. Differences in results between studies may be influenced by muscle group (proximal vs distal) and/or the methodology. For example, the age differences were more likely to be observed when at least two stimulations were used to evoke the superimposed contraction during the maximal efforts ([30]). In addition, small sample sizes (~10 participants per group) ([31–35]) and large age-related variability in activation between trials ([23,36,37]) potentially mask activation differences between young and old adults ([1]). Since 2007, several studies have also used TMS to test whether there are age-related deficits in supraspinal activation of either upper ([18,36,38,39]) or lower limb muscles ([16,40]).

Thus, the purpose of this study was to pool the results from the literature to determine via random-effects meta-analyses whether voluntary activation during MVC is lower in old compared with young adults. Given the large number of studies included in the systematic review, we were able to perform meta-analyses to evaluate the influence of age on voluntary activation across several subgroups including comparison of calculation methods (ITT vs CAR), stimulation characteristics (ES vs TMS and the stimulation number for ES studies), and muscle groups (individually and by proximity to midline). We *hypothesized* that voluntary activation would be less in old compared with young adults and more sensitive to assessment with at least two stimuli evoked during the maximal contraction. The literature was reviewed systematically to integrate all the studies assessing voluntary activation in both young and old adults.

METHODS

The present systematic review followed the Preferred Items for Systematic Reviews and Meta-analyses guidelines ([41]). Methods of the analysis and inclusion criteria were specified in advance in an International Prospective Register of Systematic Reviews protocol (CRD42016038613).

Literature search

Studies were initially identified from an electronic search performed on the bibliographic databases of MEDLINE, Web of Science, PsycINFO, and SPORTDiscus through September 2016 and an updated search was performed in April 2018. Combination of keywords (mp) and/or MeSH (/) terms related to age (Aged/, Aging/, Elderly mp, Older adult* mp), muscle activation and stimulation (Muscle activation mp, Voluntary activation mp, Central activation mp, Superimposed twitch mp) was used. Selected studies were uploaded into a screening tool (Covidence). They were first independently screened by three reviewers (V.R., A.S., C.S.) for eligibility by title and abstract and then by full text. Reference lists of included studies were also inspected, and any relevant articles not initially captured in the systematic search but met the inclusion criteria were included. Any disagreements were resolved by consensus.

Identification and selection of studies

Studies were included if they assessed voluntary activation with the ITT using either ES or TMS, or with the CAR using ES in both young (18–35 yr) and old (>60 yr; mean age, ≥65 yr) healthy participants.

Studies were required to be noninterventional; however, intervention studies were included if the baseline data could be extracted. If the required data were provided in figure format, but not numerical text, authors were contacted to obtain the numerical data. If the data could not be provided, the study was excluded to avoid potential bias due to estimation of values. No limits were placed on the year of publication. Only full-text articles published in English language were included.

Quality assessment

Risk of bias was assessed with the Quality Assessment Tool for Quantitative Studies ([42]). This standardized appraisal tool consists of six components: 1) selection bias (representation of the target population), 2) study design, 3) confounding factors, 4) blinding, 5) data collection method (validity and reliability), and 6) withdrawal (drop outs). Because the present systematic review included cross-sectional studies and baseline data from interventional studies, components 2, 3, and 4 were excluded as they are primarily related to interventional study designs ([43,44]). For each included study, components 1, 5, and 6 were rated as "strong," "moderate," or "weak" based on the detailed definitions and standardized criteria provided by the quality assessment tool ([42]). Ratings of the three components were then combined to obtain a global rating for each study ("strong," no weak ratings; "moderate," one weak rating; "weak," two or three weak ratings). Risk of bias was conducted independently by two authors, and disagreements were resolved by consensus. No studies were excluded based on the quality assessment.

To assess publication bias in the included studies, we used visual inspection of the funnel plot and the Egger's regression test to statistically quantify funnel plot asymmetry ([45]).

Data extraction and analysis

Participants' characteristics (sex, mean age, and SD or range) were identified from the selected studies. Muscle group (elbow flexors (EF), wrist flexors (WF), knee extensors (KE), plantar flexors (PF), and ankle dorsiflexors (DF)), stimulation type (ES vs TMS), stimulation number (single, paired, or train), calculation method (ITT or CAR), and results of the statistical tests were extracted. The ITT quantifies voluntary activation with the ratio between the superimposed twitch torque during an MVC and the evoked twitch torque measured at rest (or estimated using TMS) as follows: (1 − superimposed twitch/resting twitch) × 100 ([46]). CAR consists of expressing the MVC torque as a fraction of the torque produced during the superimposed contraction as follows: MVC/(MVC + superimposed torque) ([20]). Because the number of studies assessing voluntary activation during dynamic contractions was low (n = 3) and each of these studies also assessed voluntary activation during isometric contractions, only the isometric contractions were analyzed. Data including means and SD were extracted independently by three authors (V.R., A.S., C.S.), and disagreements were resolved by consensus.

Narrative synthesis

Initially, a narrative synthesis of studies was conducted. Studies were first grouped within the main results table (Table 1) based on muscle group studied (upper and lower), type of stimulation (ES or TMS), number of stimulations (single, doublet, or train), and calculation method (ITT or CAR). Studies that reported a significant difference between young and old adults were grouped together, followed by those that did not report a significant difference. The studies were then organized in descending

order based on the sample size. If studies had a similar sample size, then the studies were placed in chronological order based on the publication year from the earliest to the most recent.

TABLE 1: Included studies characteristics and results.

	Participants' Age (n)					Voluntary Activation		
Reference	Young	Old	Stimulation Method	Stimulation No.	Calculation Method	Young	Old	Significant Difference
Elbow flexors (young, 210; old, 213)								
De Serres and Enoka (48)	28 ± 5 (16)	74 ± 6 (16)	ES	Single	ITT	97.8 ± 2.6	95.0 ± 4.8	Yes
Yoon et al. (37)	21.9 ± 3.6 (15)	70.1 ± 4.3 (15)	ES	Single	ITT	97.8 ± 2.3	94.2 ± 3.6	Yes
Rozand et al. (15)	23.6 ± 4.1 (31)	69.0 ± 5.2 (31)	ES	Doublet	ITT	94.9 ± 4.1	95.7 ± 3.2	No
Klein et al. (49)	23 ± 3 (20)	81 ± 6 (13)	ES	Doublet	ITT	98.4 ± 1.8	96.9 ± 2.5	No
Allman and Rice (50)	24 ± 2 (7)	84 ± 2 (7)	ES	Doublet	ITT	97 ± 1	97 ± 2	No
Allman and Rice (51)	25 ± 2.5 (6)	84 ± 2.5 (6)	ES	Doublet	ITT	97.1 ± 1.2	97.2 ± 2.7	No
Dalton et al. (10)	24 ± 1 (6)	83 ± 4 (6)	ES	Doublet	ITT	97 ± 1	94 ± 4	No
Jakobi and Rice (23)	24 ± 1 (6)	83 ± 4 (6)	ES	Doublet	ITT	98 ± 2.7	96 ± 9.1	No
Yue et al. (24)	30.6 ± 4.3 (14)	71.4 ± 6.1 (14)	ES	Train	ITT	96.8 ± 3.7	93.7 ± 2.9	Yes
Bilodeau et al. (31)	25.5 ± 2.7 (10)	76.3 ± 5.8 (11)	ES	Train	ITT	96.6 ± 2.7	91.0 ± 5.7	Yes
Bilodeau et al. (52)	26.3 ± 3.1 (10)	70.8 ± 3.9 (9)	ES	Train	ITT	97.1 ± 3.9	94.5 ± 3.2	No
Yoon et al. (39)	21.9 ± 3.6 (14)	71.6 ± 5.4 (14)	TMS	Single	ITT	92.1 ± 4.1	87.9 ± 6.3	Yes
Hunter et al. (36)	25.5 ± 3.6 (17)	73.0 ± 3.3 (7)	TMS	Single	ITT	94.8 ± 3.4	91.2 ± 6.9	Yes
Yoon et al. (38), women	19.9 ± 1.8 (9)	73.3 ± 4.8 (20)	TMS	Single	ITT	89.4 ± 6.9	89.6 ± 9.2	No

Yoon et al. (53)	20.8 ± 2.7 (10)	73.8 ± 6.1 (16)	TMS	Single	ITT	84.9 ± 8.6	85.2 ± 11.2	No
Yoon et al. (38), men	20.8 ± 2.8 (9)	73.8 ± 6.1 (16)	TMS	Single	ITT	89.2 ± 3.5	87.2 ± 9.2	No
Molenaar et al. (18), men	25.8 ± 2.7 (5)	73.9 ± 2.7 (4)	TMS	Single	ITT	95.5 ± 2.4	96.3 ± 3.1	No
Molenaar et al. (18), women	26.5 ± 2.1 (5)	74.4 ± 0.9 (2)	TMS	Single	ITT	94.1 ± 4.1	95.4 ± 3.1	No
Wrist flexors (young, 46; old, 42)								
Clark et al. (54)	21.2 ± 3.4 (46)	70.8 ± 5.9 (42)	ES	Doublet	ITT	95.9 ± 11.7	91.5 ± 13.0	No
Knee extensors (young, 244; old, 278)								
Wilder and Cannon (55)	22.9 ± 4.3 (18)	69.3 ± 3.7 (12)	ES	Single	ITT	97.7 ± 2.3	98.2 ± 1.5	No
Bieuzen et al. (56)	25.4 ± 4.6 (10)	66.1 ± 5.8 (16)	ES	Single	ITT	91.5 ± 3.1	93.1 ± 4.4	No
Walker et al. (57)	28 ± 5 (12)	65.4 ± 4 (13)	ES	Single	ITT	96.3 ± 2.4	95.9 ± 2.9	No
Cannon et al. (58)	25.0 ± 4.0 (9)	69.8 ± 6.6 (8)	ES	Single	ITT	95.1 ± 1.7	96.2 ± 1.8	No
Mau-Moeller et al. (59)	25.3 ± 3.6 (15)	69.6 ± 3.1 (15)	ES	Doublet	ITT	91.9 ± 5.9	86.4 ± 7.7	Yes
Hvid et al. (60)	24.3 ± 0.9 (11)	67.2 ± 1.0 (11)	ES	Doublet	ITT	94.0 ± 0.8	89.2 ± 2.2	Yes
Billot et al. (61)	24.8 ± 3 (8)	68.1 ± 7.3 (8)	ES	Doublet	ITT	94.1 ± 1.9	83.6 ± 11.2	Yes
Roos et al. (29)	26.2 ± 4.1 (13)	80.0 ± 5.3 (12)	ES	Doublet	ITT	93.6 ± 3.4	95.5 ± 4.5	No
Suetta et al. (62)	21–27 (11)	61–74 (9)	ES	Doublet	ITT	91.6 ± 1.6	88.6 ± 1.6	No
Stevens et al. (63)	23.7 ± 2.1 (20)	73.2 ± 4.6 (20)	ES	Train	CAR	98.1 ± 1.7	95.5 ± 3.8	Yes
Stackhouse et al. (64)	22.7 ± 4.1 (20)	71.5 ± 5.9 (17)	ES	Train	CAR	98 ± 3	94 ± 7	Yes

Callahan et al. (65)[a]	26.1 ± 3.6 (16)	70.9 ± 4.4 (16)	ES	Train	CAR	98 ± 0	100 ± 0	Yes[b]
Solianik et al. (66), men	23.8 ± 5.0 (12)	69.6 ± 4.9 (12)	ES	Train	CAR	99.2 ± 1.4	98.9 ± 2.5	Yes
Solianik et al. (66), women	22.5 ± 1.4 (12)	72.1 ± 4.9 (8)	ES	Train	CAR	98.3 ± 2.8	92.1 ± 7.5	Yes
Miller et al. (67)	25 (12)	75 (20)	ES	Train	CAR	98 ± 4	96 ± 7	No
Sundberg et al. (16)	22.6 ± 2.2 (30)	72.8 ± 7.6 (73)	TMS	Single	ITT	97.7 ± 2.1	96.4 ± 4.0	No
Souron et al. (40)	28 ± 6 (15)	65 ± 5 (8)	TMS	Single	ITT	95.2 ± 2.6	88.8 ± 2.5	No
Plantar flexors (young, 148; old, 151)								
Akagi et al. (68), men	22 ± 2 (20)	73 ± 5 (19)	ES	Single	ITT	93.3 ± 7.3	85.6 ± 9.4	Yes
Akagi et al. (68), women	22 ± 1 (20)	72 ± 7 (14)	ES	Single	ITT	88.5 ± 10.8	86.6 ± 7.5	Yes
Scaglioni et al. (35)	26 ± 4 (11)	76 ± 3 (13)	ES	Single	ITT	97.4 ± 2.6	96.8 ± 3.3	No
Dalton et al. (33)	24.1 ± 2.8 (10)	77.5 ± 3.0 (10)	ES	Single	ITT	98.3 ± 2.9	97.1 ± 4.8	No
Dalton et al. (69)	26.3 ± 3.4 (10)	83.7 ± 11.3 (10)	ES	Single	ITT	96.4 ± 2.7	95.6 ± 2.6	No
Kirk et al. (70)	27 ± 3 (10)	81 ± 4 (10)	ES	Single	ITT	98.7 ± 1.4	98.1 ± 2.6	No
Unhjem et al. (71)	22 ± 2 (9)	73 ± 6 (11)	ES	Single	ITT	90 ± 6	84 ± 5	No
Dalton et al. (72)	23.5 ± 2.9 (6)	75.3 ± 4.1 (6)	ES	Single	ITT	99.2 ± 0.7	99.0 ± 0.7	No
Morse et al. (25)[a]	24.7 ± 4.7 (14)	73.6 ± 3.7 (21)	ES	Doublet	ITT	98.6 ± 0.1	78.1 ± 3.2	Yes
Barber et al. (73)	27 ± 3 (18)	70 ± 3 (16)	ES	Doublet	ITT	90.4 ± 10.7	89.6 ± 14.4	No
Simoneau et al. (27)	23.9 ± 1.7 (11)	77.1 ± 1.8 (12)	ES	Doublet	ITT	94.7 ± 6.9	90.0 ± 12.5	No

Morse et al. (25)	24.7 ± 4.7 (9)	73.7 ± 3.6 (9)	ES	Doublet	ITT	98.6 ± 3.0	93.1 ± 12.3	No
Dorsiflexors (young, 142; old, = 144)								
Power et al. (74)	24.8 ± 3.2 (9)	76.0 ± 5.5 (9)	ES	Single	ITT	99.2 ± 1.0	99.6 ± 1.3	No
Power et al. (75)	25.5 ± 3.7 (8)	76.1 ± 5.4 (9)	ES	Single	ITT	99.2 ± 1.8	99.7 ± 0.8	No
Ryan et al. (76)	22.6 ± 1.9 (18)	69.2 ± 4.9 (19)	ES	Doublet	ITT	93.1 ± 1.2	92.1 ± 1.4	No
Connelly et al. (9)	20.8 ± 0.8 (6)	82.0 ± 1.7 (6)	ES	Doublet	ITT	99.3 ± 0.1	99.1 ± 0.2	No
Klass et al. (17) men[a]	25.4 ± 3.2 (10)	78.7 ± 5.7 (10)	ES	Doublet	CAR	100 ± 0	100 ± 0	No
Klass et al. (17), women[a]	25.9 ± 4.4 (10)	74.6 ± 5.7 (9)	ES	Doublet	CAR	100 ± 0	100 ± 0	No
Kent-Braun and Ng (77)	32 ± 5 (24)	72 ± 5 (24)	ES	Train	CAR	96 ± 10	99 ± 5	No
Kent-Braun et al. (78), men[a]	33.5 ± 6.5 (10)	74.4 ± 5.3 (11)	ES	Train	CAR	100 ± 0	98 ± 3	No
Kent-Braun et al. (78), women	32.3 ± 4.8 (10)	75.0 ± 5.9 (10)	ES	Train	CAR	100 ± 3	99 ± 3	No
Chung et al. (32)	26 ± 5 (12)	72 ± 4 (12)	ES	Train	CAR	100 ± 1	99 ± 2	No
Lanza et al. (34)[a]	26 ± 4 (9)	72 ± 4 (9)	ES	Train	CAR	100 ± 0	100 ± 0	No
Russ et al. (79), women[a]	25.0 ± 4.2 (8)	72.6 ± 4.2 (9)	ES	Train	CAR	98 ± 5	100 ± 0	No
Russ et al. (79), men[a]	24.3 ± 5.9 (8)	73.7 ± 3.3 (7)	ES	Train	CAR	100 ± 0	100 ± 1	No

Values are mean ± SD. Fifty-four studies and 61 data sets (data from seven studies were separated between men and women) were included in the systematic review.

*a*Studies not included in the meta-analysis because 1) SD was 0 in at least one of the participant groups or 2) the age-related difference in voluntary activation was greater than 3 SD above the mean (one study). *b*Greater activation in old compared with young adults.

Meta-analysis pooled and subgroup analysis

To support the narrative synthesis, a meta-analysis of pooled data and subgroup analyses were conducted. Initially, effect sizes were calculated for each study using a general inverse variance method and weighted using Cohen's *d* for differences in voluntary activation between young and old participants. Thresholds for small, moderate, and large effects were set at 0.2, 0.5 and 0.8, respectively. Data were pooled with both fixed (inverse-variance method) and random effects (DerSimonian and Laird method) models. Although both models returned similar main effects, we only reported the results of the random-effects analyses because there was significant heterogeneity between studies.

To assess heterogeneity between studies, I^2 tests were performed. Heterogeneity was classified as low (I^2 = 25%–50%), moderate (I^2 = 50%–75%), or high ($I^2 \geq 75\%$) using classification criteria suggested by Higgins et al. ([47]). Initially, the entire sample was included within a single model. To determine the origins of heterogeneity, subgroup analyses were conducted on both individual muscle groups and anatomical location (proximal and distal), calculation method (ITT and CAR), stimulation method (ES and TMS), and ES number (single, doublet and train of stimuli). Potential sources of publication biases were also explored with funnel plots.

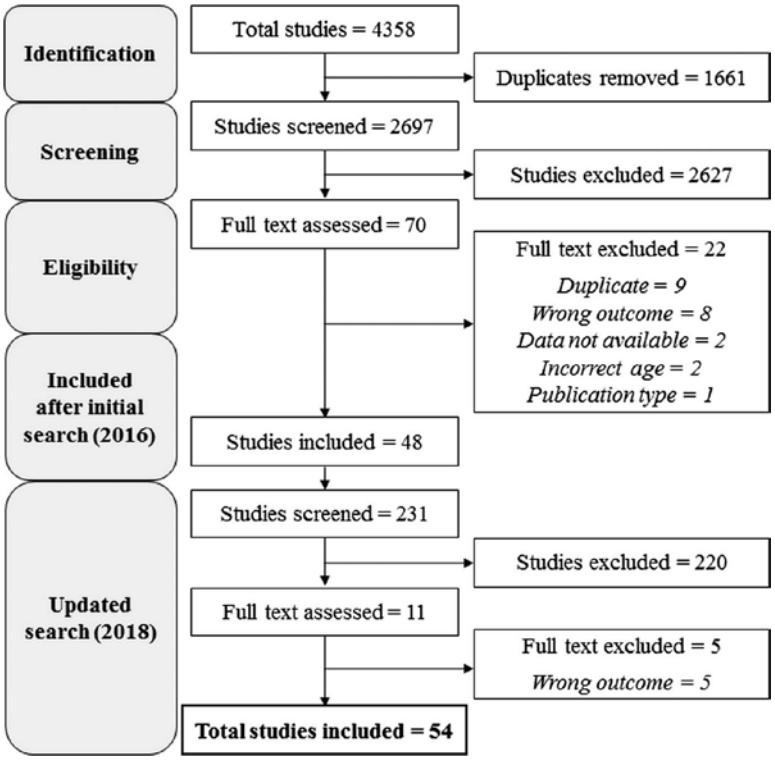
All meta-analyses and subgroup analyses were undertaken using the metan function in STATA v14 (V.14; STATA Corp.) The *a priori* level of significance for all comparisons was $P < 0.05$. Pooled data are presented as (Cohen's *d* standardized mean difference (SMD; 95% confidence intervals); z-statistic, *P* value) unless otherwise indicated.

RESULTS

Study Selection

A total of 4358 studies were initially identified from the preliminary search (Fig. 1). After an automatic removal of duplicates (*n* = 1661), 2627 studies were excluded from the titles and abstracts. Of the 70 remaining full-text studies, 22 studies were excluded for various reasons including the following: duplicates not identified in the previous steps (*n* = 9), voluntary activation that was not assessed using the ITT or CAR (*n* = 8), voluntary activation data were not available in the text and the authors could not be contacted (*n* = *2*), mean age did not meet the inclusion criteria for the older group (*n* = 2), or the publication was not a research article (*n* = 1). The second search conducted on April 2018 revealed six extra articles that met the inclusion criteria. Fifty-four studies were included in the narrative synthesis and meta-analysis. Within these 54 studies, 7 presented the data from men and women separately, and so were considered separately for synthesis and analyses, resulting in 61 data sets. The Preferred Items for Systematic Reviews and Meta-analyses flow diagram is presented in Figure 1.

FIGURE 1: PRISMA flowchart of the study selection.



Study Characteristics: Narrative Synthesis

Table 1 provides a summary of the 54 included studies and 61 data sets. The publication year ranged from 1998 to 2018. A total of 790 young (mean age ranged from 20 to 34 yr) and 828 old (mean age ranged from 65 to 84 yr) participants were included in the selected studies, resulting in a mean sample size of 15 young (range from 6 to 46) and 15 old (range from 6 to 73) participants. In both young and old participants, most of the participants were men (68.0% and 67.1%, respectively), and 27 studies were composed of men only, whereas only one study was exclusively women.

Voluntary activation was assessed in five muscle groups: EF (*n* = 16 studies), KE (*n* = 16), PF (*n* = 11), DF (*n* = 10) and WF (*n* = 1). Three studies also assessed voluntary activation of the elbow extensors in addition to the EF, but the data were not included in the analysis because they were obtained from the same subjects in the two muscle groups. The majority of studies used ES (*n* = 47), and a smaller portion used TMS (*n* = 7). For TMS, voluntary activation can only be calculated using the ITT with single stimulation. For ES, experimenters used single (*n* = 15), doublet (*n* = 19), and train (*n* = 13) stimulations on both upper and lower limb muscles. Voluntary activation was calculated using the ITT with single (*n* = 15), doublet (*n* = 18), and train (*n* = 3) stimulations, and CAR with train stimulations (*n* = 10) and doublet stimulations (*n* = 1).

Thirty-nine of the 54 studies did not observe significant age-related differences in voluntary activation (70% of the sample size), 14 observed a greater activation in young (28% of the sample size) compared with old adults, and 1 study reported greater voluntary activation in old compared with young adults. For the EF, KE, and PF, some studies showed age-related differences, whereas others did not. However, all the studies targeting the DF showed no difference between young and old adults. Only a few studies (2/22; 11% of the sample size) observed a greater activation in young compared with old adults for

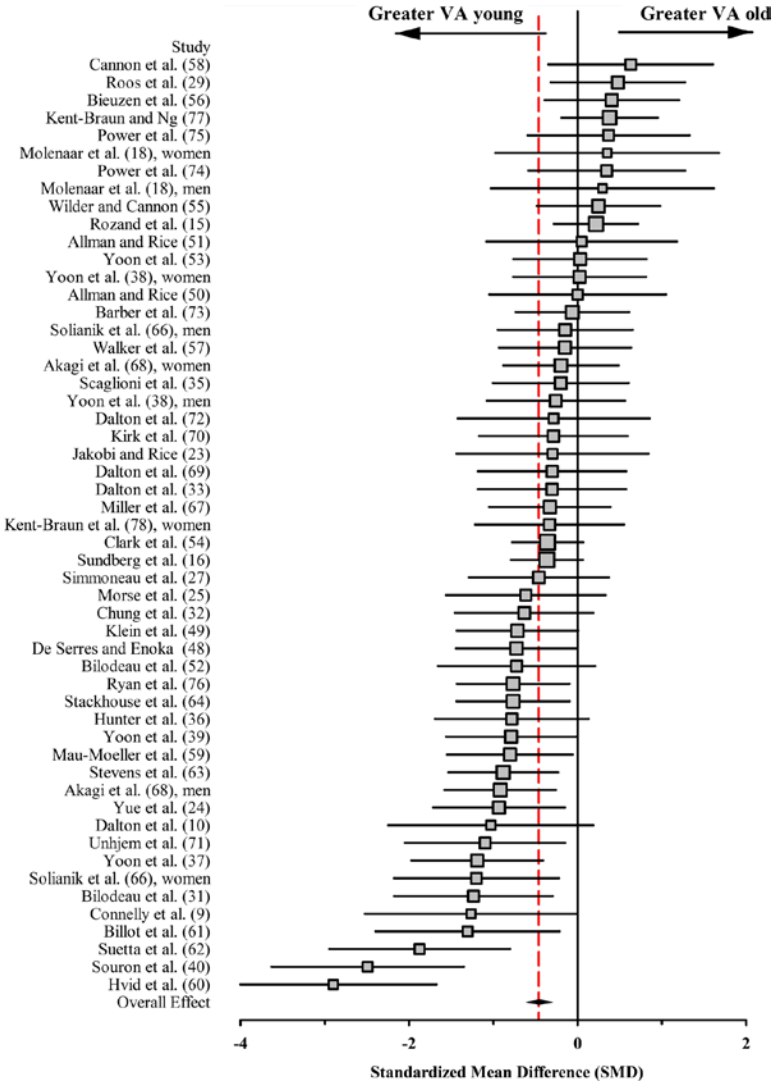
distal muscles (DF, PF, WF), whereas 12 of 32 studies (37% of the sample size) reported greater activation in the young for proximal muscles (EF, KE).

Pooled Analysis: Total Studies

Fifty-four studies with 61 data sets were initially included in the quantitative synthesis. One study was excluded from analyses because the age-related difference in voluntary activation (young greater than old) was greater than 3 SD above the mean. Seven data sets reported 100% activation, with an SD of 0 in at least one of the participant groups, which did not allow for calculation of effect sizes. To enable inclusion of these studies in the meta-analysis, a small variance of 0.01 was added as the SD to groups reporting an SD of 0, and meta-analyses were run with the entire sample. The meta-analysis was conducted both with and without the added variance. The results of the meta-analyses both with and without the added variance did not differ, and so only the meta-analyses without the added variance are reported (n = 53 data sets).

Figure 2 presents the forest plot for all included studies in the quantitative synthesis. When considering all studies together, voluntary activation was greater in the young compared with the old (−0.45 (−0.62 to −0.29); z = 5.46, P < 0.001). However models were also moderately heterogeneous with I^2 values of 52.4% (P < 0.001), indicating that the dispersion could be due to parameters such as muscle group involved, calculation method of voluntary activation, stimulation method and/or stimulation number used.

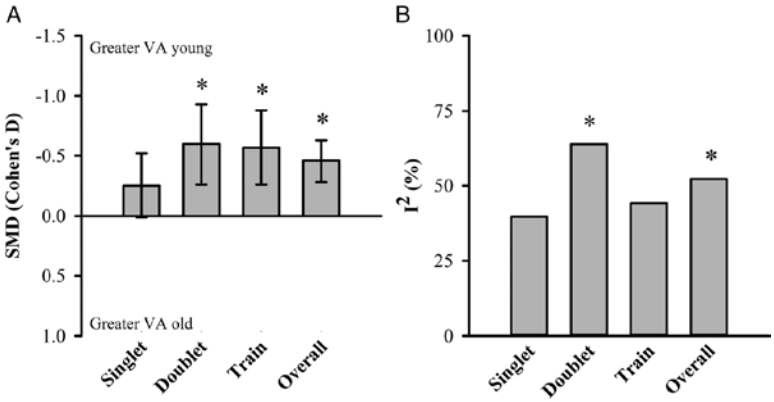
FIGURE 2: Forest plot displaying random-effects meta-analysis of voluntary activation in young and old adults. The vertical dashed line represents the mean overall effect. Symbol size reflects the weight of the effect for each individual study (based on random-effects analysis). Symbols on the left of the continuous black line at 0 show greater mean voluntary activation (significant or not) in young compared with old adults, whereas studies on the right reflect greater mean activation in old adults than in the young adults.



Subgroup Analysis: By Stimulation Number for ES

Comparison of single, doublet and train stimulations for studies using ES revealed greater voluntary activation in young compared with old adults (Fig. 3). However, this only reached significance for doublet (−0.60 (−0.93 to −0.52); $z = 3.49$, $P < 0.001$) and train stimulations (−0.57 (−0.88 to −0.26); $z = 3.56$, $P < 0.001$) but not single stimulation (−0.26 (−0.52 to 0.01); $z = 1.86$, $P = 0.06$). Heterogeneity was moderate for doublet stimulations (63.9%) and low for single (39.8%) and train stimulations (44.2%).

FIGURE 3: Subgroup analysis displaying random-effects meta-analysis (A) and heterogeneity (I^2 test; B) by stimulation number for ES superimposed during the maximal contraction. Negative SMD indicates greater voluntary activation in the young adults than in the old adults. Heterogeneity is considered as low ($I^2 = 25\%–50\%$), moderate ($I^2 = 50\%–75\%$), or high ($I^2 \geq 75\%$). *$P < 0.05$.

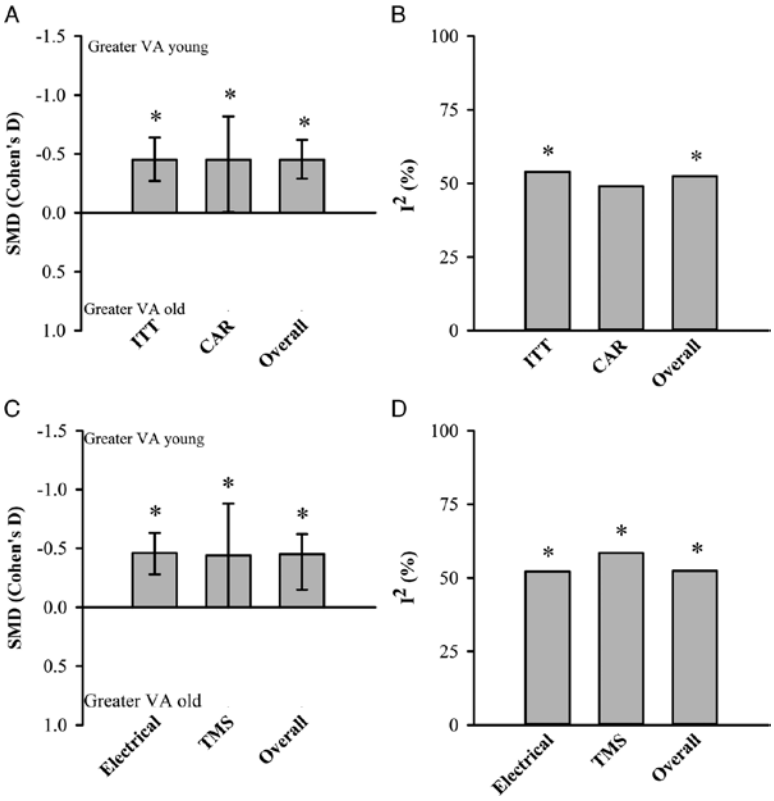


Subgroup Analysis: By Calculation Method and Stimulation Method

ITT versus CAR

Subgroup analyses comparing the age differences in studies using the ITT and CAR revealed greater voluntary activation in young compared with the old for both the ITT (−0.45 (−0.64 to −0.27); z = 4.88, $P < 0.001$) and CAR techniques (−0.45 (−0.82 to −0.00); z = 2.39, P = 0.01). Heterogeneity was low for the CAR method and moderate for the ITT method (Fig. 4). It should be noted that CAR has been used for the KE and DF only, and all the studies using CAR on the DF were performed by the same research group. In addition, CAR was used with electrical train stimulations (only one study with doublet stimulations), whereas ITT was used with single and doublet ES and TMS.

FIGURE 4: Subgroup analysis displaying random-effects meta-analysis and heterogeneity (I^2 test) of voluntary activation by calculation method (A, B) and by stimulation method (C, D). Negative SMD indicates greater voluntary activation in young compared with old individuals. Heterogeneity is considered as low (I^2 = 25%–50%), moderate (I^2 = 50%–75%), or high (I^2 ≥ 75%). *$P < 0.05$.



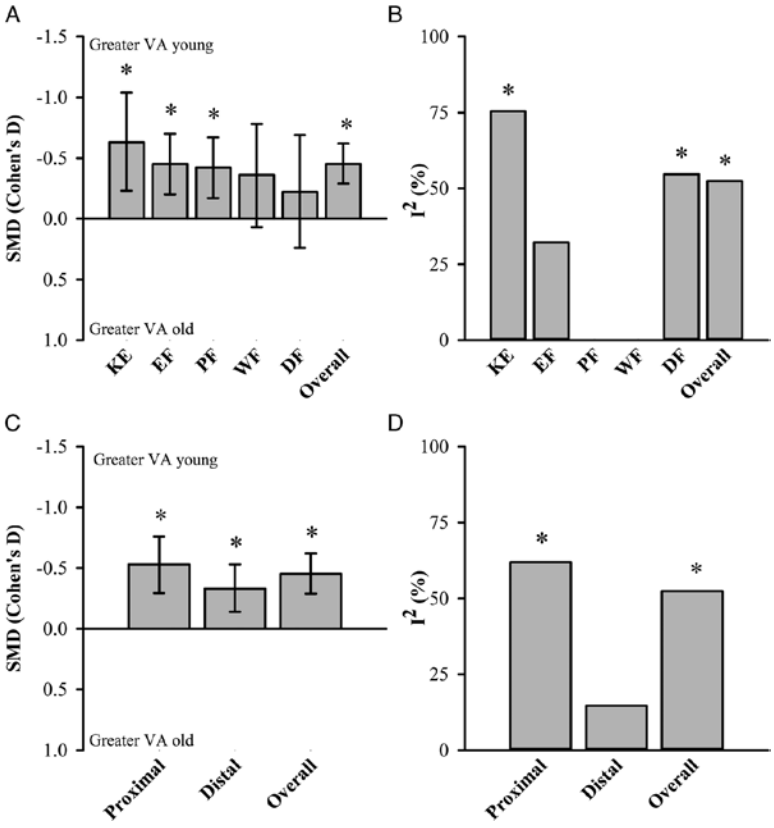
ES versus TMS

Voluntary activation was greater in the young compared with old for both ES (−0.46 (−0.63 to −0.28); z = 5.03, P < 0.001) and TMS (−0.44 (−0.88–0.00); z = 1.07, P = 0.049). Although the SMD was similar for the two stimulation methods, the 95% confidence interval was much greater for TMS, probably due to the fewer number of studies using this stimulation method (Fig. 4). Heterogeneity was moderate for both methods (ES: 52.2%; TMS: 58.4%).

Subgroup Analysis: By Muscle Group and Proximity

Subgroup analysis by muscle group revealed greater voluntary activation in the young compared with the old for the PF (−0.42 (−0.67 to −0.17); z = 3.33, P < 0.001), KE (−0.63 (−1.04 to −0.23); z = 3.09, P = 0.002) and EF (−0.45 (−0.70 to −0.20); z = 3.54, P < 0.001), but not for DF or WF (Fig. 5). It should be noted that only one study involved the WF, so the main effect should be interpreted with caution. Overall, when all muscle groups were pooled, the heterogeneity was moderate (54.4%) and varied between muscle groups. The EF reported low heterogeneity (32.2%), the KE had high heterogeneity (75.5%), and the DF had moderate heterogeneity (54.6%). To explore if heterogeneity was driven by the inclusion of TMS studies in the analysis, ES studies were considered separately. Similar to those mentioned previously, young adults showed greater voluntary activation compared with the old for both KE (−0.55 (−0.98 to −0.12); z = 2.50, P = 0.01) and EF (−0.58 (−0.93 to −0.24); z = 3.32, P = 0.001). Heterogeneity was moderate for KE (73.5%) and EF (44.5%).

FIGURE 5: Subgroup analysis displaying random-effects meta-analysis and heterogeneity (I^2 test) of voluntary activation by individual muscles (A, B) and by muscle proximity (C, D). Negative SMD indicates greater voluntary activation in young compared with old individuals. Heterogeneity is considered as low (I^2 = 25%–50%), moderate (I^2 = 50%–75%), or high (I^2 ≥ 75%). *P < 0.05.



Muscle subgroup analysis separated by distal (DF, PF, WF) and proximal muscles (EF, KE) revealed a greater voluntary activation in the young compared with the old adults for both distal (−0.33 (−0.53 to −0.14); z = 4.45, P < 0.001) and proximal (−0.53 (−0.75 to −0.29), z = 3.38, P < 0.001) muscles (Fig. 5). Heterogeneity was low for distal muscles (14.6%) and moderate for proximal muscles (61.9%).

Risk of Bias

Critical appraisal was globally moderate. All the studies scored strong on data collection methods as they all used the ITT or CAR equations. All the studies but five scored strong on drop outs. However, only nine studies scored moderate on selection bias and the others scored weak, as we did not consider the selected individuals to be representative of the population. Indeed, the young participants were often recruited within the university and/or the older adults were usually community-dwelling people living at a reasonable distance from the university.

Publication bias was assessed using a funnel plot (Figure, Supplemental Digital Content, Funnel plot of the SE and standardized effect for each study, http://links.lww.com/MSS/B790). Visual inspection of the funnel plot shows that three studies fall below the 95% confidence interval, whereas five studies are above. Egger's regression test suggests that there is no significant asymmetry of the plot (intercept = −1.37, P = 0.07).

DISCUSSION

This meta-analysis determined the effect of age on voluntary activation in healthy adults during maximal isometric contractions. Based on the meta-analysis involving 790 young (18–35 yr) and 828 old (mean age, ≥65 yr) adults, voluntary activation was lower with aging during MVC for the KE, EF, and PF muscles. When all muscle groups were included, there was a moderate heterogeneity due, at least in part, to the age-related differences between muscle groups and the number of stimulations used to assess voluntary activation. Other factors such as physical activity levels or methodological issues not identified here such as the number of MVC trials may play a role in this heterogeneity. Voluntary activation was lower in old compared with young adults for all muscle groups except the DF, and with both ES and TMS for the muscles tested with the two methods. Importantly, the age deficit in voluntary activation was significant for electrically evoked paired stimulus and trains of stimuli, but there was no overall age difference for the single stimulus. These findings suggest that healthy old adults have a reduced ability to maximally activate their muscle during isometric contractions than young adults in most muscle groups investigated, and that single electrical stimulations may not be sensitive enough to detect age-related differences in voluntary activation.

Age-related decrease in voluntary activation

The meta-analysis showed that old adults exhibited a reduced ability to voluntary activate several large muscle groups including the KE, PF, and EF muscles compared with young adults during MVC. The effect was consistent across most techniques with differences between muscle groups and methods discussed hereinafter. The large age-related variability in activation within and between old adults ([1]) possibly masks some of the age-related changes present in studies with smaller sample sizes. The reduced voluntary activation with aging may be attributed to variability in age-related impairments within the central nervous system and activation between the motor cortex and motor units ([1,7,80]). Functionally, corticospinal excitability is altered with aging in some muscles ([81,82]), although not all

muscles ([83]). Spinal cord responsiveness can also be less with aging in part due to decreased sensitivity of muscle spindles ([84,85]). There is also a net loss of motoneurons with aging, possibly originating from instability of the neuromuscular junction ([7,86]). Old adults exhibit lower discharge rates of motor units during maximal and submaximal contractions compared with young adults in some muscles and a reduced recruitment range of motor units ([8,11,12]). Together, such age-related changes could lead to reduced activation in healthy old adults during maximal voluntary contractions. We found, however, that the age-related deficits were not ubiquitous across muscles, the effect was modest and was influenced by the specifics of the technique.

Methodological considerations and age-related differences in voluntary activation

Our results indicate that the age-related differences in activation were similar when assessed with TMS and ES for the EF and KE muscles and confirm recent experimental findings where activation was compared between young and old adults using both methods with the EF muscles ([15]). TMS has been used in more recent years to quantify voluntary activation, specifically supraspinal drive, in young and old adults ([16,18,36,39]). The similar age-related reduction in voluntary activation with both ES and TMS suggests that some of the deficit in activation could originate from a suboptimal motor output from the motor cortex. However, the meta-analysis showed larger 95% confidence intervals for TMS than ES, probably due to the limited number of studies using TMS in old adults and predominantly on the upper limb muscles.

Importantly, we found that the age-related deficits in voluntary activation were detected with paired and train stimulations but not with a single stimulation. Although several studies reported that a single stimulation can detect less than optimal activation (e.g., Ref. [[37]]), its sensitivity is thought to be more limited when comparing differences between groups and conditions ([87–89]), which is supported in this meta-analysis. Heterogeneity was greater with paired stimuli compared with trains of stimulation ([90,91]), although stimulation trains will increase discomfort for the participant ([90]) with the increased likelihood of inhibition of voluntary force ([19]). The greater heterogeneity with paired stimuli may be explained by the greater number of muscle groups assessed with this technique (EF, WF, KE, PF, and DF) compared with train stimuli (KE and DF) and the lower number of studies and research groups using train stimuli. Paired stimulations are a reasonable compromise between reliability and discomfort in evaluating voluntary activation in young and old adults.

The meta-analyses showed that both ITT and CAR methods for quantifying voluntary activation were able to detect an age-related reduction in voluntary activation for the KE and EF muscles despite proposed differences in sensitivity between the techniques ([17,90,92,93]). The CAR method that uses a train of stimulation has only been used to test for age differences in activation in the KE and DF. Because several studies that tested the DF reported 100% activation in their cohorts ([34,78,79]), we performed the meta-analysis with and without the CAR. We found no difference in the age deficits of activation with or without the inclusion of the CAR studies. Furthermore, the heterogeneity for the ITT and CAR in these muscles was similar.

Age effects in different muscle groups

The age-related difference in activation was muscle dependent with age-related deficits in the EF, KE, and PF muscles but not in the DF. The age-related differences in voluntary activation were also present

whether the muscle group was located proximally or distally. The discrepancy in the age-related difference in activation between muscle groups may be because of their functional and physiological/histological differences ([80]) rather than whether they are located proximally or distally ([30]). For example, age-related slowing of muscle contractile properties was observed to be greater for the DF than the KE, although the motor unit discharge rates during contractions at different levels of force were similar in young and old men for the KE, and lower with age for the DF ([9,94]). Thus, it is possible that old adults may achieve high levels of voluntary activation in the DF muscles with lower levels of descending drive than young adults. Alternatively, the minimal age differences in DF muscle may be due to methodological issues in assessing this muscle group. Inadvertent activation of the antagonist muscles is possible when stimulating the fibular (peroneal) nerve and will lower the evoked interpolated force during maximal effort. This would overestimate voluntary activation ([19,89]) so that the activation was near 100% (as seen in some studies; Table 1), and thus minimize possible age differences.

In addition, the differences in voluntary activation between muscles exist in young adults ([95]) with lower activation in the KE compared with the EF, PF, and DF. In older adults, between-subject variability and trial-to-trial variability can be large ([15,23,36]) and possibly explain the reduced activation compared with young adults. Jakobi and Rice ([23]) showed that older adults were able to activate their EF at a similar level to the young adults when the best trial was considered. However, the average activation over 10 trials was much lower in the old because of a greater inconsistency in maximal performance compared with the young, and certainly, practice can aid in achieving best results ([1,36]). The greater variability in activation among the old adults across maximal effort trials was not likely due to age differences in force steadiness because older adults are less steady than young primarily at low submaximal forces ([96,97]). For both young and old adults, when the stimulation does not occur at peak force during the maximal effort, a correction can be applied ([98]) so as not to underestimate voluntary activation. Rather, it is more likely that the older adults are more variable in achieving optimal activation on a trial-to-trial basis than young adults ([99]).

One other consideration not accounted for in this analysis is the age range within the old adults that was relatively large (mean, 65–84 yr). It is well known that the deficits in muscle function are accelerated in very old age (~80 yr) ([100–102]). We were not able to separate the studies within older group based on age because of the small number of studies that tested very old adults (>80 yr) ([16]). Understanding whether voluntary activation deficits are even greater in very old adults (>80 yr) than old adults (65–79 yr) presents an opportunity for future research.

Is the age-related difference in voluntary activation meaningful?

The general age-related difference in voluntary activation during the isometric MVC seems modest compared with the decrease in muscle mass in healthy older adults (for reviews, see Refs. [[1,2]]) and raises the question of the significance of this age-related difference in activation. One possibility is that a small deficit in voluntary activation can represent a much larger reduction in strength, except in subjects with a very high ability for maximal activation ([103]). Although the age-related difference in voluntary activation is modest, its effect on strength may be underestimated based on a linear relationship between activation and percentage of maximal voluntary force rather than with a curvilinear relationship ([26,104]). Furthermore, several studies indicated that even healthy old adults are

more variable in their ability to activate their muscles, with more practice and familiarization needed to achieve similar levels to that of young adults ([1,15,23,36]). Other factors such a low level of physical activity that is common with increased age will lower voluntary activation ([105]) and probably increase variability between old adults ([1]). Given that real activities typically involve one attempt at a task, more variable activation could result in less adequate and more variable activation in even healthy old adults.

Lastly, the studies reviewed in this meta-analysis involved healthy old adults without known disease. Old adults volunteering to participate in research studies are likely to be more physically active than the general population of similar age. Larger deficits are more certain in older populations that have a clinical diagnosis as has been seen in older adults who have a history of falling ([106]), osteoarthritic knees ([107]), and stroke ([108]) as examples. Thus, it is possible that age-related deficits in activation in general the population may be greater than the moderately small effects we exhibited in this meta-analysis.

CONCLUSIONS

This systematic review incorporated 54 studies investigating voluntary activation in ~800 young and ~800 old subjects. Old adults showed a modest reduction in voluntary activation compared with young adults for all the muscles investigated, except the DF. Importantly, age-related deficits in voluntary activation were only detected when paired or multiple electrically evoked stimuli were used, highlighting the importance of the method used to assess activation. Because voluntary activation is influenced by various parameters, future studies should systematically specify the physical activity level of the participants, the number of trials and whether a familiarization was performed. More studies should also investigate age-related changes in voluntary activation during moderate to fast dynamic contractions in different muscle groups that reflect the activity of the muscles during daily life activities.

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