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Review Article

Neuromuscular Contributions to Age-Related Weakness

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\textbf{Background.} Declines in skeletal muscle mass and quality are important factors contributing to age-related weakness. Neural activation of agonist and antagonist muscles may also be important contributing factors.

\textbf{Methods.} We conducted a review of the scientific literature on older adults to determine (a) methodologies used to quantify activation, (b) the potential role of agonist and antagonist activation on weakness, and (c) some possible neurophysiological mechanisms that may underlie impaired activation.

\textbf{Results.} The cumulative evidence indicates that agonist activation is impaired in some, but not all, older adults and that this impairment contributes to age-related weakness. It is possible that antagonist coactivation also plays a role in age-related weakness, though a definitive link has not been established.

\textbf{Conclusion.} Future research should focus on improving quantitative measurement and mechanistic understanding of impaired activation with aging.

\textbf{Key Words:} Strength—Electromyography—Skeletal muscle—Nervous system.

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THE well-described decline of skeletal muscle mass in older adults is a critical determinant of age-related weakness, which we define as reduced maximal voluntary joint torque or power production. Yet it is now clear that the relationship between weakness and muscle size in older adults is less robust than once believed (1). Indeed, longitudinal studies of older adults indicate that maintenance or even gain of muscle mass may not prevent weakness (2,3). Furthermore, there are a number of age-related changes in torque production capability that are not readily explained by a reduction in muscle mass, including reduced specific torque (torque per cross sectional area) (4,5) and slower rate of isometric torque production (expressed relative to peak torque or to body weight) (6,7). These findings may be at least partially accounted for by reduced intrinsic force-generating capacity or “muscle quality,” due to factors such as altered muscle fiber contractile and metabolic properties (8,9), accumulation of intramuscular lipids (5), and alterations in excitation–contraction coupling (10). Furthermore, the transfer of force between the muscular and skeletal systems may be affected by age-related changes in muscle architecture (11) and in the length and compliance of tendons (12,13).

In addition to factors related to skeletal muscle mass and contractile function, a critical component of the weakness observed with aging may be altered neuromuscular activation. For the purpose of the present review, we define neuromuscular activation (henceforth referred to as “activation”) as the process by which muscular force is elicited via recruitment and rate coding of motor units. The goal of this brief review is to provide an introductory overview of the methodologies used to quantify activation, the contribution of agonist and antagonist activation to weakness, and some possible neurophysiological mechanisms that may underlie impaired activation in older adults. Throughout this review, we focus predominantly on studies that examine muscles of the lower extremity in order to maximize relevance to the serious problem of age-related mobility disability.
Quantifying agonist neuromuscular activation

Electromyography (EMG), T2-weighted magnetic resonance imaging (T2 MRI), and muscle electrical stimulation are the techniques that are most widely used for evaluating whether agonist activation can be maximized by volitional effort. Each technique has unique limitations, and there is not a clear “gold standard” approach to quantifying incomplete activation at this time.

EMG measures the electrical activity in motor neurons and muscle fibers during muscle contraction. The two major classifications are indwelling EMG and surface EMG (sEMG). Indwelling EMG involves inserting very thin wires into the muscle tissue to record motor neuronal recruitment and firing rates. The information recorded is only a small representation of the cumulative motor unit activity that occurs throughout the muscle, so it is not possible to estimate the extent of whole-muscle activation with this technique. sEMG involves placing a pair of electrodes on the skin over the muscle of interest in order to record the net electrical activity of the motor units and muscle fibers within the electrode detection area. sEMG must be interpreted carefully as there are a variety of confounding factors that challenge the ability to compare activation parameters across subjects, sessions, and tasks (14). These factors include, but are not limited to, the placement of the electrode relative to the underlying muscle fibers, the amount of subcutaneous adipose tissue between the muscle and electrodes, detection of activation from muscles that were not intended to be recorded (ie, “crosstalk”), and signal cancellation (ie, amplitude reduction) due to asynchronous firing of action potentials. The error associated with these factors can be reduced by normalizing sEMG amplitude to that recorded during a reference contraction (15) or to maximal M-wave amplitude (16). Non-normalized sEMG amplitude may also provide valuable information in studies that are well controlled and have sufficient sample size (eg, see (17–19)). Unlike the muscle electrical stimulation and T2 MRI techniques, indwelling EMG and sEMG generally cannot be used to detect impaired activation in an individual person due to the limitations described earlier that affect signal amplitude and timing. Rather, impaired activation is typically detected by comparing activation parameters between an experimental and control group (eg, old compared with young) or within the same group pre- and postintervention.

T2 MRI estimates activation by evaluating the exercise-induced increase in nuclear magnetic resonance transverse relaxation time (T2) of muscle water (20). Stated simply, muscle tissue that has been more active appears brighter on a T2-weighted image compared with muscle tissue that has been less active. Numerous studies have documented an associated between sEMG and T2 amplitude, suggesting that activation is a primary driver of this phenomenon (for one example, see (21)). An advantage of T2 MRI over sEMG is that it can simultaneously provide a three-dimensional whole-muscle estimate of activation from all relevant muscles. Disadvantages of this approach include potential inaccuracy due to the indirectness of the methodology (ie, estimating activation from shifts in muscle water), issues with cost and access to an MRI scanner, and the need to conduct the measurement while the participant is at rest following the activity of interest.

Muscle electrical stimulation involves delivering a single, dual, or train of electrical pulses to the motor axons of the agonist muscle(s) during a maximal voluntary effort contraction. Complete voluntary activation of the muscle is assumed if no additional torque is evoked, whereas incomplete activation is evident by the presence of a torque increment. This approach is valuable for indicating the presence of incomplete activation, though its validity as a sensitive quantitative index has been questioned due to evidence that it overestimates voluntary activation capability (22,23). Furthermore, direct comparison of electrical stimulation with T2 MRI (24) and sEMG (25) indicates that electrical stimulation has poor sensitivity to changes in torque and activation levels, particularly as voluntary effort approaches maximum. In the quadriceps of young adults, the electrical stimulation approach generally indicates complete or nearly complete voluntary activation during a maximal voluntary isometric contraction (MVC). In contrast, T2 MRI studies have estimated that MVC torque in young adults can be achieved by activating just 70%–75% of the muscle (24,26).

Furthermore, a number of studies have shown that sEMG during fast isokinetic contractions is considerably higher than during MVC (17,27–29) and slow contractions (30) in young or middle-aged adults. Accordingly, it appears that the muscle electrical stimulation technique has relatively poor ability to detect markedly incomplete quadriceps activation during an MVC (though this may differ for other muscle groups). Reflex inhibition is likely responsible for this incomplete agonist activation (30) (see section on “Spinal Reflex Pathways”), which further suggests that the isometric contraction mode may not be ideal for the purpose of assessing the integrity of voluntary (ie, corticospinal) neural drive.

Evidence linking impaired neuromuscular activation to age-related weakness

A number of studies using indwelling EMG have reported reduced maximal motor unit discharge rates in agonist muscles with aging (6,31–34), and some studies show that these findings are related to deficits in maximal torque production (6,33,34). Deficits in torque and power have also been linked to reduced maximal rate of agonist sEMG rise (Figure 1) in older adults >70 years compared with those ≤70 years (35), in older adults who are less active compared with those who are highly active (7), and in older adults who have limited mobility function compared with those with high mobility function (36). Decrements in rate of sEMG rise occur despite evidence that peak sEMG amplitude during sustained MVCs is relatively preserved with
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Aging (16,17,36,37). Greater impairment of sEMG at the onset of rapid contractions compared with during maximal sustained contractions is consistent with the widely reported finding that rapid dynamic torque generation (ie, power) is more impaired than slow or isometric torque generation (38–41). Resistance training studies in older adults also provide strong evidence of the link between strength and activation as quantified using both sEMG (increased amplitude (19,42) and maximal rate of rise (43)) and muscle electrical stimulation (44) paradigms.

The effect of aging on agonist sEMG amplitude during dynamic contractions is less clear. Similar sEMG amplitudes have been reported in old and young adults (16,37) and in old and middle-aged adults (17). However, during fast concentric contractions, sEMG amplitude and torque production have been shown to be lower in older adults compared with young adults (45) and in older adults with mobility limitations compared with older adults with high-mobility function (17) (Figure 2).

To our knowledge, T2 MRI has not yet been used to assess age-related activation deficits, but muscle electrical stimulation has been used extensively. A recent review by Klass and colleagues (46) summarizes the findings from muscle electrical stimulation studies as being inconclusive, with some studies reporting no activation deficit (37,47) and some reporting mild-to-moderate (ie, up to about 11%) activation deficits (48,49) in healthy older adults compared with younger adults. Larger activation deficits have also been reported, including an average deficit of 22% in the plantarflexors of recreationally active older adults (4) and 19% in the knee extensors of old adults with limitations in performance of activities of daily living (50).

The influence of age-related changes in antagonist muscle coactivation is another factor that could conceivably contribute to weakness through mechanical opposition of the action of the agonist (51) and due to reciprocal inhibition of the agonist (see section on “Spinal Reflex Pathways”). However, the evidence on whether antagonist coactivation is (17,19,38,52) or is not (4,16,37,45,53) elevated during maximal effort contractions is inconclusive. Furthermore, the methodological approach that is generally used to assess coactivation has limitations. Most studies quantify coactivation using either a ratio of antagonist activity to agonist activity (19,37) or a ratio of antagonist activity during the task of interest to activity of the same muscle when it acts as an agonist during an MVC (17,38,52). In both cases, the finding of heightened coactivation ratios in older adults could be misleading. In the former case, low agonist sEMG amplitude might contribute to a higher coactivation ratio (eg, see (19)). In the latter case, low maximal sEMG amplitude of the antagonist muscle when it acts as an agonist during an MVC might contribute to a higher coactivation ratio (eg, see (52)). More relevant than sEMG ratios is the amount of resistive torque produced by the antagonist. We know of only one study that has estimated antagonist torque in older and younger adults, and it shows that antagonist torque is actually lower in older adults (53). Although other studies have not explicitly examined antagonist torque production, some do report age-related impairment of net joint torque production but no difference in coactivation (4,16). This seems consistent with the premise of lower torque production by both the agonist and the antagonist muscles. Also, our recent data indicate that torque...
production during rapid isokinetic knee extension is associated with agonist activation (17) (Figure 3A) but not with antagonist coactivation (Figure 3B) across a sample of middle-aged and older adults. Cumulatively, there is a lack of definitive evidence that antagonist coactivation substantially contributes to weakness in older adults.

**PHYSIOLOGY OF IMPAIRED ACTIVATION IN OLDER ADULTS**

**Corticospinal Pathway**

Reduced excitability in the corticospinal pathway may lead to compromised ability to control muscular force production (54). Corticospinal excitability is often assessed by transcranial magnetic stimulation, a noninvasive technique in which a localized magnetic field elicits action potentials in cortical neurons. These action potentials can be recorded peripherally as a motor-evoked potential (MEP) by sEMG. The stimulator intensity at which MEPs of sufficient amplitude are generated consistently is called the resting or active motor threshold depending on whether the muscle is tested at rest or during a submaximal contraction, respectively (55). Motor threshold is a common measure of corticospinal excitability as is the MEP amplitude at a particular intensity of stimulation (which is defined within each study).

Transcranial magnetic stimulation studies in older adults are inconclusive with regard to whether active motor threshold is increased (less corticospinal excitability) (56) or unchanged (57,58) in older adults compared with young adults. However, evidence indicates that older adults have a smaller MEP amplitude than young adults at a specified level of stimulus intensity (57,58) and that older adults require more stimulation to elicit the same maximal MEP amplitude (59). In addition to motor threshold and MEP amplitude, other transcranial magnetic stimulation measures such as the cortical silent period and paired pulse paradigms may be helpful for understanding the excitatory and inhibitory balance of intracortical circuits (57,58). To our knowledge, transcranial magnetic stimulation measures of corticospinal excitability have not definitively been linked to voluntary activation capability in older adults. However, stimulation of the motor cortex can elicit torque increments during MVC in younger and older adults, suggesting that corticospinal excitability plays a role in activation deficits (60).

**Spinal Reflex Pathways**

Motor neuronal activation is influenced by a large number of spinal reflex pathways, and it is possible that changes in these pathways with aging may influence voluntary force production. Reciprocal inhibition, which is mediated by activation of Ia inhibitory interneurons, modulates agonist–antagonist coactivation and may be altered with aging. For instance, a smaller reduction of agonist sEMG in response to electrical stimulation of the antagonist has been observed in older adults (61). This mechanism may account for changes in coactivation reported with aging (62), though an effect of this phenomenon on voluntary torque production has not been established. Recurrent inhibition occurs when an agonist motor neuron is inhibited by a recurrent branch of its own axon, which first synapses with a Renshaw interneuron. We found only one study examining resting recurrent inhibition levels in young and older adults, with no significant differences found (63). Autogenic inhibition also inhibits agonist motor neurons via inhibitory interneurons that are activated in response to tension at the musculotendinous junction (64). It has been proposed as a mechanism to limit excessive stress on the musculoskeletal system (30,65,66) and may influence voluntary agonist activation during high force contractions (eg, during MVC). We know of no studies that have examined age-related changes in autogenic inhibition.

Given the prevalence of osteoarthritis and other musculoskeletal issues with aging, weakness in some people may be explained by arthrogenous inhibition, which is impaired activation associated with joint pathology. Pain may play a role in this mechanism (67,68) such that joint discomfort is minimized by inhibitory reflex responses and/or conscious avoidance of high force production. However, pain does not fully account for arthrogenous inhibition (67), indicating that disease-related sensorimotor impairments may also alter motor neuron excitability (69).

**Motor Unit**

Aging is known to result in the presence of fewer larger motor units due to death of motor neurons (70) and subsequent collateral sprouting of the remaining motor neurons to reinnervate the abandoned muscle fibers (71). However, this motor unit remodeling may not lead to weakness until a critical threshold of motor neuron loss is reached (72). Slowing of various motor neuronal properties has also been observed in older adults. Other than reduced maximal motor neuron
firing rates (as mentioned earlier), other factors include a reduction in motor neuron conduction velocity (73) and reduced occurrence of motor neurons firing two action potentials in quick succession (ie, “doublets”) (6,74). Age-related changes in agonist motor neuron firing behavior may result from compromised central drive and altered intrinsic mechanisms and have been linked to weakness (6,33,73).

Neuromuscular Junction

The neuromuscular junction is responsible for electrochemical transmission of the neural command for muscle contraction. The integrity of the neuromuscular junction is known to decline with aging (75,76), which may impair communication between the nervous and muscular systems (eg, excitation–contraction uncoupling) and limits force production (10). Furthermore, molecular activity between motor neurons and muscles has been shown to occur in both directions, indicating that the neuromuscular junction plays a role in maintaining the integrity of both structures (10).

Influence of Participant Characteristics on Research Findings

Age-related physiological change of neuromuscular function is not a linear process and is likely influenced by various biological and behavioral factors (eg, genetics, nutrition, physical activity level, comorbidities, etc.). These factors contribute to heterogeneity among older adults, which challenges the ability to understand what neuromuscular deficits are inherent to aging. To minimize the confounding effects of this heterogeneity, investigators should carefully control and report the characteristics of their research participants. Of the relevant articles cited in this review (Table 1), approximately 70% reported performing a medical screening (beyond reporting absence of neuromuscular disease), 63% reported specific screening criteria for physical activity levels or actually recorded physical activity, 52% provided information on body composition, and 11% administered a functional assessment. It is possible that some studies performed these procedures but omitted the details from the published article. Our recent work shows that administering a functional assessment can be valuable for identifying older individuals with higher and lower neuromuscular function. We categorized healthy community-dwelling older adults into two groups based primarily on Short Physical Performance Battery score (≥10 vs ≤9 points, out of 12 maximum points). The lower functioning group exhibited marked weakness and impaired agonist activation compared with the higher functioning group (17,36). This finding suggests that an activation

Table 1. Information Provided by Cited Articles about Research Participant Characteristics

<table>
<thead>
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<th>Mean Age: “Older” Group(s)</th>
<th>Mean Age: “Younger” Group</th>
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<th>Physical Activity Screening†</th>
<th>Body Composition‡</th>
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Notes: N/A, not applicable. *Reported screening for medical conditions (beyond absence of neuromuscular disease). †Reported physical activity screening criteria and/or recorded physical activity. ‡Reported body composition information (at minimum, group average weight and height).
deficit may contribute to emerging declines in mobility function. Yet in most studies, it is likely that the participants in these distinct groups would have been merged into a single heterogeneous older group, thus obscuring potentially valuable insight into the neural determinants of weakness and physical function.

CONCLUSIONS

The cumulative evidence indicates that neuromuscular activation of the agonist is impaired in some but not all older adults and that weakness is more prominent in those with impaired activation. The role of antagonist coactivation in age-related weakness has not been definitively established. Additional research is needed to improve the methodological approaches used for detecting and monitoring abnormal agonist and antagonist activation. There is also a need to elucidate the specific mechanisms within the central and/or peripheral nervous system that contribute to activation impairment, so that interventions can be targeted to the appropriate source(s).

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