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Age-Related Changes in Motor Cortical Properties and Voluntary Activation of Skeletal Muscle

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Abstract

Aging is associated with dramatic reductions in muscle strength and motor control, and many of these age-related changes in muscle function result from adaptations in the central nervous system. Aging is associated with wide-spread qualitative and quantitative changes of the motor cortex. For example, advancing age has been suggested to result in cortical atrophy, reduced cortical excitability, reduced cortical plasticity, as well as neurochemical abnormalities. The associated functional effects of these changes likely influence numerous aspects of muscle performance such as muscle strength and motor control. For example, there is evidence to suggest that the muscle weakness associated with aging is partially due to impairments in the nervous system's ability to fully activate motor neurons- particularly in the larger proximal muscle groups. In this review article we discuss age-related changes in the motor cortex, as well as the ability- or lack thereof- of older adults to voluntarily activate skeletal muscle. We also provide perspectives on scientific and clinical questions that need to be addressed in the near future.

Keywords

Aging; dynapenia; sarcopenia; muscle; motor cortex; strength; weakness; motor control; atrophy; elderly

INTRODUCTION

It is well established that aging is associated with dramatic reductions in muscle strength (dynapenia) and motor control [1, 2]. For example, data from the most recent longitudinal aging study suggest that muscle strength decreases at a staggering rate of ~ 3%/year between the ages of 70–79 years [3]. The resultant muscle weakness is independently associated with the development of disability [4], impairment of functional capacity [5–7], fall risk [8], and even mortality [9].

The decline in maximal voluntary force production in the elderly is associated with a number of alterations in the properties of both skeletal muscle and the nervous system [1]. Specifically, aging has been associated with a variety of changes in the neuromuscular system that theoretically would reduce maximal voluntary force. Changes include reduced cortical and spinal excitability [10–14], altered motor unit discharge properties [15–18],

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reduced motor unit size and numbers [19, 20], reduced muscle mass (sarcopenia) [3, 21, 22], slowing in whole muscle contractile properties and cross-bridge cycling [23–26], impaired excitation-contraction coupling [27–29], and decreased tendon stiffness [30, 31]. With the rapidly advancing age of our society it is critical that the scientific community develop a better understanding of these aging-related changes in neuromuscular anatomy and physiology so that therapeutic targets and effective interventions can be developed to ameliorate the reduction in muscle function. Many of the aforementioned facets of age-related changes in muscle and nerve biology are discussed in the other articles appearing in this special journal issue. In the present review article we will discuss age-related changes in the motor cortex, as well as the effects of aging on voluntary activation of skeletal muscle. The aging process exerts differential effects on specific areas of the brain, and many neurodegenerative diseases and conditions can modify many of the age-related neurologic adaptations. Here, we will delimit our discussions of the brain to changes primarily associated with 'normal aging' of the sensorimotor system.

AGE-RELATED CHANGES IN THE MOTOR CORTEX

Aging and Motor Cortex Morphology & Neurochemistry

The neurons in the pre-motor and motor cortex form a complex network of glutamatergic interneurons, afferent projections, and pyramidal neurons that project to several areas of the central nervous system that include the striatum and spinal cord. Although it is often widely assumed that there is a progressive loss of motor cortical neurons in normal aging, it does not appear that an actual loss of neurons occurs *per se* [32, 33]. With that stated, there are an overwhelming number of morphometric changes in the motor cortex that do occur in with normal aging. For example, cadaveric dissections from humans who died without neurological signs suggest that individuals over 65 years of age exhibit a 43% volumetric reduction in the premotor cortex neuron perikaryon (cell body) size in comparison to adults younger than 45 years [32]. These early cadaveric observations have more recently been corroborated in living humans using high-resolution structural magnetic resonance imaging (MRI) [34]. In this latter work Salat *et al*. (2004) obtained MRIs from 106 non-demented individuals ranging in age from 18 to 93 years and calculated thickness of a number of different areas of the cortex to examine regional atrophy. These findings revealed that cortical thinning occurs by middle age, and that areas near the primary motor cortex (e.g. precentral gyrus) demonstrate prominent atrophy [34] (Fig. **1**). In addition to changes in the overall size of the motor cortex there is also evidence to suggest that age-related differences exist in white matter mass and length of myelinated nerve fibers [35]. Specifically, Marner and colleagues examined brain tissue from 36 individuals ranging in age from 18 to 93 years whose cause of death or previously diagnosed diseases were not associated with the central nervous system. Based on these cross-sectional findings that suggested that individuals lose ~ 45% of their total length of myelinatedfibers in the brain white matter, with this reduction being particularly pronounced in the smallest nerve fibers [35]. Furthermore, cross-sectional studies also suggest that aging disrupts white matter integrity[36]. From a functional standpoint it seems likely that these age-related changes would affect cortico-cortical and corticospinal connectivity.

In addition to morphological changes in the aging brain, there has long been interest regarding the effects of aging on neurochemical related changes- particularly those within the basal ganglia. This interest was largely driven by the idea that changes in neurotransmitters and their receptors may be associated with the decrease in both cognitive and motor functions- thus predisposing older adults to certain diseases/conditions. Indeed, impaired neurotransmission is responsible for at least some of the behavioral abnormalities associated with aging, as illustrated by Arvid Carlsson's Nobel winning work indicating that depletion of dopamine from the substantia nigra and neostriatum underlies the motor deficits

in Parkinson's disease [37]. “Normal” age-related changes have also been observed in the serotonergic [38, 39], cholinergic [40], adrenergic [39], dopaminergic [41–44], GABAergic [41, 43], and glutamatergic systems [41, 43], as well as in reductions in neurotrophic factors within the motor cortex [45].

Age-related changes in the dopaminergic system are perhaps the best understood- as there has been enormous scientific interest on this topic due to the functional relationship of dopamine mediating aspects of manual dexterity. Older adults have been reported to exhibit reduced dopamine transporter availability [46], and animal findings indicate that older rodents have decreased dopamine receptors (namely the D_2 receptor) [47]. The reduction in D_2 receptors has been mechanistically linked to the gene level as mRNA for the receptor has been reported to be 50% less in older animals [48]. Most recently scientists have begun to examine the complex reciprocal modulation of neural transmission among a number of neurotransmitters during aging. Some of the more interesting findings are the reports of age-related changes in the interactions between glutamate, dopamine, and GABA in the nucleus accumbens, which plays a role in emotion and motivation as well as in motor behavior and has been postulated to be associated with the reduction in volitional physical activity observed in the elderly [43].

Aging and Motor Cortex Excitability, Activity, and Plasticity

In addition to the age-related anatomical and cellular changes as discussed above, aging also affects motor cortical properties at the systems level. Specifically, aging has been shown to result in cortical hypoexcitability [11, 13, 49, 50], increased activation in areas of sensory processing and integration during motor tasks [51–53], and a reduced cortical plasticity [54, 55]. In the next few paragraphs we will briefly summarize some of the evidence pertaining to these respective changes.

The effect of aging on cortical excitability is most commonly examined using transcranial magnetic stimulation (TMS), which also allows for the assessment of cortico-cortical facilitation and inhibition [56, 57]. A recent investigation on age-related changes in intracortical facilitatory and inhibitory properties using paired-pulse TMS suggests that middle-aged adults exhibit reduced cortical excitability in comparison to younger adults, as it has been observed that individuals in their late 50’s and early 60’s exhibit more intracortical inhibition and less intracortical facilitation than adults in their twenties [11]. Our recent findings in the elderly (mean age of 71 years) support these previous data, as we have observed that older adults exhibit substantially more intracortical inhibition and less intracortical facilitation in comparison to young adults [50] (Fig. **2**).

Aging-related changes have also been observed with respect to the spatial activation patterns of sensorimotor areas of the brain during motor tasks [51–53]. Investigations of this nature most commonly utilize functional magnetic resonance imaging (fMRI) to quantify the hemodynamic response in the brain (changes in blood flow and oxygenation) as an indirect measure of neural activity during given motor tasks [58]. These studies have revealed that older adults commonly exhibit additional activation in areas that perform sensory and motor processing during standardized motor tasks [51–53], particularly on the ipsilateral side [52]. One recent article of particular interest to neuromuscular physiologists investigated the effects of aging on the fMRI blood oxygen level dependent response during handgrip contractions of varying intensities [59]. Here, Ward and colleagues observed that the motor cortex of older adults is less able to increase activity when increased handgrip force is required [59].

In addition to age-related changes in excitability and activity, the human motor cortex also displays an age-dependent reduction in cortical plasticity [54, 55]. For example, Fathi *et al*.

reported that electrical stimulation of the median nerve at the wrist (paired-associative stimulation) resulted in an increased amplitude of the motor evoked potential elicited using TMS in young (21–39 yrs) and middle-aged (40–59 yrs), but not in older adults (60+ yrs) [54]. Collectively, these findings suggest that aging results in reduced motor cortical excitability, a loss of functional asymmetry, reduced ability to modulate the activity of inappropriate motor networks when required, and attenuated cortical plasticity- all of which may contribute to age-related reductions in motor performance.

AGE-RELATED CHANGES IN MAXIMAL VOLUNTARY MUSCLE ACTIVATION

As stated earlier, aging is commonly associated with muscle weakness. This loss of muscle strength is likely due to a wide-variety of physiologic reasons, including reductions in muscle mass and changes in the excitation-contraction coupling process. However, it is also probable that a portion of the strength loss is attributable to cortical mechanisms, and the nervous systems ability-or lack thereof- to fully activate skeletal muscle. For example, the loss of muscle strength is substantially greater than the loss of muscle mass associated with aging, and this dissociation suggests that other explanatory mechanisms beyond muscle atrophy influence weakness [1]. Further, from a functional perspective, low levels of muscle strength, but not muscle mass, are independently associated with disability development [4], functional capacity [5, 60], and even mortality [9]. Thus, it is imperative that scientists and clinicians understand the role of the central nervous system in mediating the loss of muscle strength observed with age.

There is evidence to suggest that aging results in impaired agonist activation and/or increased antagonistic coactivation [61]; however, age-related differences in voluntary activation appear to vary between muscle groups. Prior to more fully discussing the effects of aging on voluntary activation we will first provide a brief overview of the assessment of voluntary activation. Voluntary activation has been defined as the level of voluntary drive during an effort [62, 63]. A voluntary effort, or a voluntary contraction of a muscle, comprises the recruitment of motor neurons, and hence muscle fibers, by increased descending drive. With an increased force of contraction there is increased activation of neurons in the primary motor cortex with increased firing of corticospinal neurons (for review see [64]). The larger this descending drive, the greater the number of motor neurons recruited in the spinal cord and the faster they fire. Each motor neuron innervates a number of muscle fibers that fire one-to-one with the motor neuron. Together, these comprise a motor unit. When a motor unit fires sufficiently fast, its muscle fibers produce a fused contraction. While there are many influences on motor neurons during voluntary contractions, such as excitatory and inhibitory sensory feedback, and alterations in motor neuron properties that may make them more or less responsive to synaptic input [65], descending drive from the motor cortex is the major determinant of the timing and strength of voluntary contractions.

Voluntary activation is commonly assessed using the interpolated twitch method, or a derivative thereof (e.g., central activation ratio) [62, 66]. Here, the motor nerve to the muscle is electrically stimulated during a voluntary effort. During maximal voluntary efforts, any increment in force evoked by a stimulus indicates that voluntary activation is less than 100%. That is, some motor units are not recruited or are not firing fast enough to produce fused contractions [67]. The extra force evoked by stimulation during contraction can be quantified by comparison to the force produced by the whole muscle. Thus, voluntary activation represents the proportion of maximal possible muscle force that is produced during a voluntary contraction. Measurement of voluntary activation does not quantify the descending drive reaching the motor neurons, nor whether motor neuron firing rates are

maximal, nor does it take into account the source of drive to the motor neurons. However, mechanisms in the cortex, spinal cord and muscle can all influence voluntary activation (e.g [62]). Recently, transcranial magnetic stimulation has also been used to estimate voluntary activation during maximal voluntary contractions. Here, when an increment in force is evoked it indicates that output from the motor cortex was not sufficient to drive the motor neurons to drive the muscle maximally but that some motor cortical output remained untapped by the subject's voluntary effort [68].

When maximal voluntary activation is compared between muscles, conditions or subjects, it is important to remember that the ability to generate maximal force or power depends on the properties of the muscle as well as on the absolute output from the nervous system. For example, muscle fibers that have slower contraction and relaxation rates require slower firing rates to generate their maximal force (e.g. [69, 70]).

There are a number of changes in the motor pathway with aging that might be expected to influence voluntary activation but it is difficult to predict the overall result of these changes on the ability to activate the muscle maximally. It seems likely that drive to the motor neurons is reduced. Alterations in the motor areas of the cortex, as detailed above, may lead to decreased or poorly focused descending drive, and single motor unit responses show a reduction in the effect of corticospinal input to the motor neurons [71]. In addition, sensory feedback from the muscle is altered. A reduction in the sensitivity of muscle spindles is likely to decrease their excitatory drive to the motor neurons during contraction [72, 73]. However, there are also changes in the population of motor neurons with fewer large neurons seen in the ventral horn [74, 75]. This is attributed to a loss of large motor neurons, which usually have the highest threshold for recruitment and innervate the largest and fastest muscle fibers. This shift should tend to reduce the excitatory drive needed to recruit motor neurons. At the same time, there is a shift in muscle fiber properties with a greater proportion of slower fibers in most muscles [76, 77]. This change should also reduce the required drive for maximal voluntary activation.

Aging and Voluntary Activation: Effect of Muscle Group and Physical Condition

There are equivocal reports in the literature on whether or not advancing age reduces voluntary activation capacity (Fig. **3**) [69, 78–95]. A synthesis of the literature however does provide some insight into potential explanations of these equivocal reports. As shown in Fig. **3**, several studies examining the effect of age on voluntary isometric activation of the knee extensors (Fig. **3A**) and the elbow flexors (Fig. **3B**) suggest that older adults, particularly those greater than 70–75 yrs of age, exhibit a decrease in voluntary activation; whereas investigations on the age-related changes in voluntary activation of the dorsiflexors yield null findings (Fig. **3C**). Due to the functional differences between these muscles, as well as differences in their physiologic profiles (e.g. motor unit innervations and fiber type characteristics) these muscle-group specific effects are not overly surprising. Differences in activation of different muscle groups are reported in young subjects [96]. The knee extensors are generally reported as less well activated whereas the ankle dorsiflexors are reported as fully activated surprisingly often [97]. Aging may amplify these intermuscle differences in activation. For example, slowing of muscle contraction and relaxation with age is greater for the ankle dorsiflexors than the knee extensors [69, 77]. Consistent with this difference, motor unit firing rates recorded during contractions of different forces show similar rates in young and old men for the knee extensor, vastus lateralis, but slower rates for old men than young men for the ankle dorsiflexor, [69, 77]. This suggests that for the ankle dorsiflexors, old adults may be able to achieve high levels of voluntary activation with levels of output from the nervous system that are lower than those in young adults, whereas similar output in young and old is required for the knee extensors. Muscle slowing in upper limb muscles, including the elbow flexors, is also reported as minor (~10%) [77].

Figure **3B** shows that the studies that have measured the ability to drive the elbow flexors maximally present relatively homogenous results. Voluntary activation is consistently reported as 1%–5% lower in the older adults than in the young adults, and this difference is significant in over half the studies [78, 82, 84, 85, 95, 98]. One study highlighted here (Fig. **3B**, vertical arrow) was conducted by Jakobi and Rice [85]. While the authors only examined a small number of younger and older subjects (n=6/group, mean ages: 24 and 83 years), they did observe a novel and interesting finding: that voluntary activation is less consistent across trials in older men compared to younger men. Specifically, they observed that no differences existed between younger and older adults when voluntary activation was compared based on the single best attempt/trial (e.g., the trial with the highest level of voluntary activation) (98 vs. 96%). However, when voluntary activation was calculated based on an average of ten attempts/trials a dramatic age-difference was observed, with younger adults consistently achieving high levels of voluntary activation (95%) whereas older adults only achieved voluntary activation levels of ~79%. Similar inconsistency between trials and between individuals has also been noted in later studies [84, 98]. It is notable that Hunter *et al*. [84] used transcranial magnetic stimulation to measure voluntary activation, which implies that the cause of the variable performance may be supraspinal. These findings suggest that while similar peak levels of voluntary activation may be achievable by old and young subjects, aging results in greater variability in attaining maximal voluntary activation - at least in the elbow flexor muscles.

With respect to studies on the knee extensors, a number of reports show no differences between old and young adults, but two reports stand out as showing a deficit in voluntary activation with aging (Fig. **3A**, vertical arrows) [83, 85, 93]. The first of these highlighted studies was conducted by Harridge and colleagues [83]. This study examined the oldest cohort of individuals that, to our knowledge, has been examined to date (n=11, age range: 85–97 years). Here, it was observed that very old adults display significant impairment in central activation- with a mean knee extensor voluntary activation level of only 81% (range: 69–93%). These findings suggest that deficits in the neural drive can contribute to much of the muscle weakness observed in the very elderly - at least in the knee extensor muscles. Unfortunately, no direct comparison was made with young adults, but voluntary activation of the knee extensors measured with twitch interpolation is generally reported as 85%–95% [97]. The second of the highlighted studies is an article by Stevens and colleagues that combined previously collected data sets on the effect of aging on knee extensor voluntary activation [93]. This study deserves particular attention because it is the largest to date (young adults: n=46, 18–32 years, older adults: n=46, 64–84 years). Here, measured voluntary activation fell from ~98% to ~94%. However, the curvilinear relationship between measured voluntary activation and the percentage of maximal voluntary force was then taken into account (as opposed to assuming a linear relationship as is most common). With this correction, the voluntary activation of older adults was calculated to produce 87% of maximal muscle force in comparison to 98% maximal force produced by younger subjects. These findings are interesting because they demonstrate that clinically meaningful deficits in voluntary activation do exist in the knee extensors when a population of older individuals is considered. In addition, they emphasize that a relatively small deficit in measured voluntary activation may represent a much larger deficit in force production (see also [99]). Together, the studies of Stevens *et al.* (2001) and Jakobi and Rice (2002) underscore the need to critically consider the methodological approach used to quantify voluntary activation (for further discussion of this topic the reader is referred to articles by Klass *et al*. [61] and Taylor *et al.* [63]. Relatively minor methodological differences (e.g. measurement of average or peak activation; degree of familiarisation with the task) may underlie some of the inconsistent results across studies.

PERSPECTIVES AND CONCLUSIONS

Over the last 20 years, through initiatives such as the Decade of the Brain (1990–1999) and the Bone and Joint Decade (2002–2011), our understanding of the aging neuromuscular system has dramatically increased. For example, we have learned that normal aging is associated with widespread qualitative and quantitative changes in grey matter and white matter [34–36], as well as in neurochemical abnormalities [39, 41–44]. These changes are particularly noted in areas of the brain associated with the sensorimotor system. Additionally, recent data suggest that older adults exhibit reduced motor cortical excitability [11, 13, 57], increased activation in areas of sensory processing and integration during motor tasks [51–53], and a reduction in cortical plasticity and adaptability [54, 55]. The associated functional effects of these changes likely influence numerous aspects of muscle performance- including muscle strength, fatigability and control, although the magnitude of effect may be muscle group specific. For example, while there is some discrepancy in the literature, there is evidence to suggest that the muscle weakness associated with aging is partially due to impairments in the nervous system's ability to fully activate motor neurons [83, 85, 93]. This evidence is particularly strong for the elbow flexors. There is also evidence for a deficit in activation of the knee extensors, which are clinically important as their level of muscle strength has been linked to disability development and functional capacity [5, 100].

In looking to the future there are still several critical scientific issues to be addressed. For instance, the vast majority of studies to date investigating changes in cortical properties and neuromuscular function have employed cross-sectional designs, and longitudinal studies are needed to better determine the true effects of aging. Additionally, studies aimed at investigating differences in sub-populations of older adults are needed, such as studies of the pre-frail and frail elderly, as well as those with mild cognitive declines. With respect to cognitive aspects, a recent study observed that poor physical function and muscle strength coexisted with cognitive impairment, and that this relationship was independent of muscle mass and physical activity level [101]. Accordingly, this finding raises the question of the interrelationship between neural activation of muscle and cognitive function, and further work is needed to better understand these associations. In addition, there are more clinically-oriented questions to be addressed, especially in light of the dramatic increase in the total number of older adults that will occur over the next 20 years [102]. Particularly critical questions surround the influence of lifestyle factors on the age associated chages in the neuromuscular system, as well as the development of effective and practical interventions or pharmacologic agents to promote and maintain neuromuscular function.

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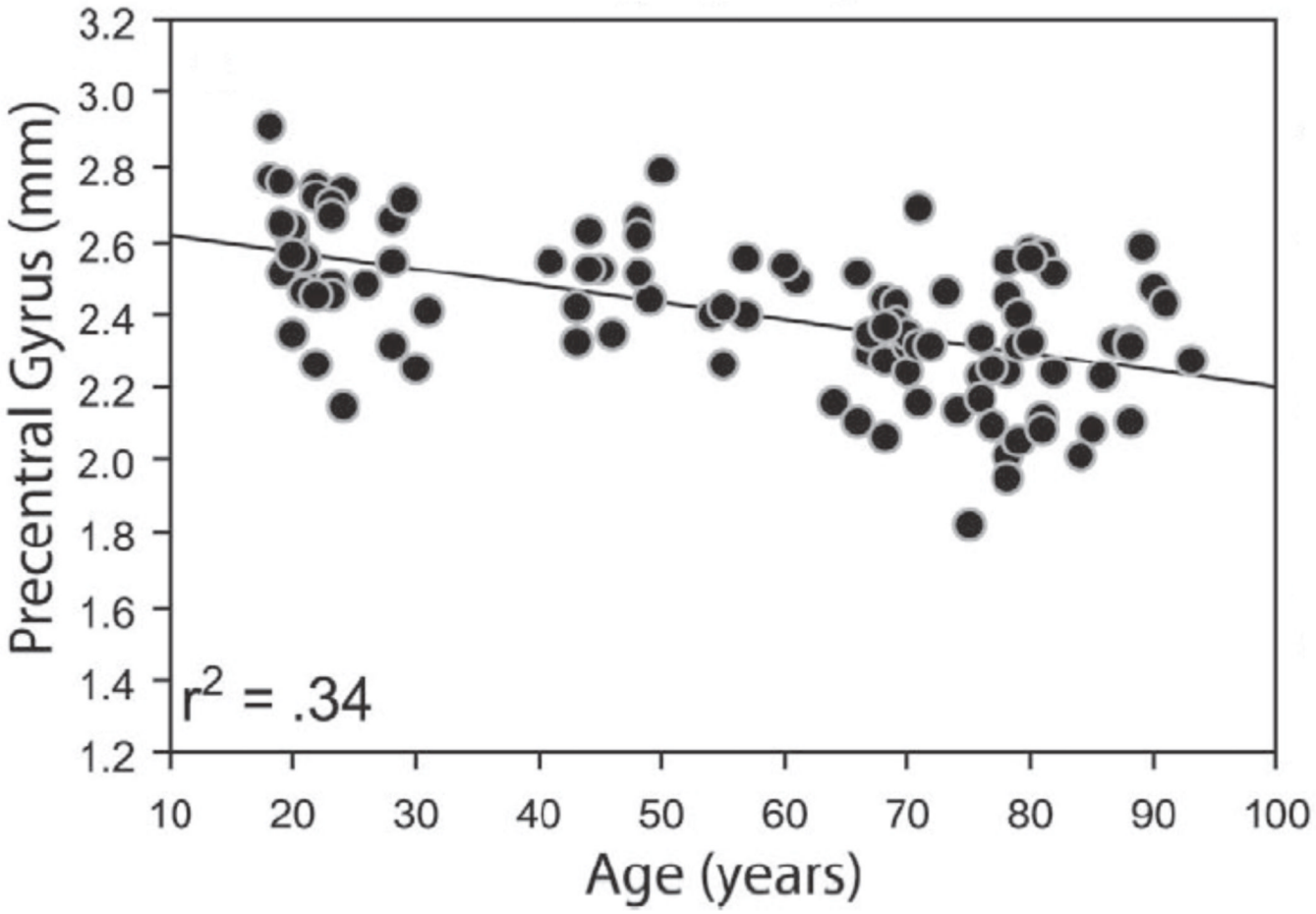

Fig. (1). Age-associated atrophy of the precentral gyrus

These data represent thickness values of the precentral gyrus obtained *via* high-resolution MRI from over 100 individuals ranging in age from 18–93 years. Overall there was significant thinning of the precentral cortex, and regression analyses indicated that age explained 34% of the between-subject variability in precentral gyrus thickness.

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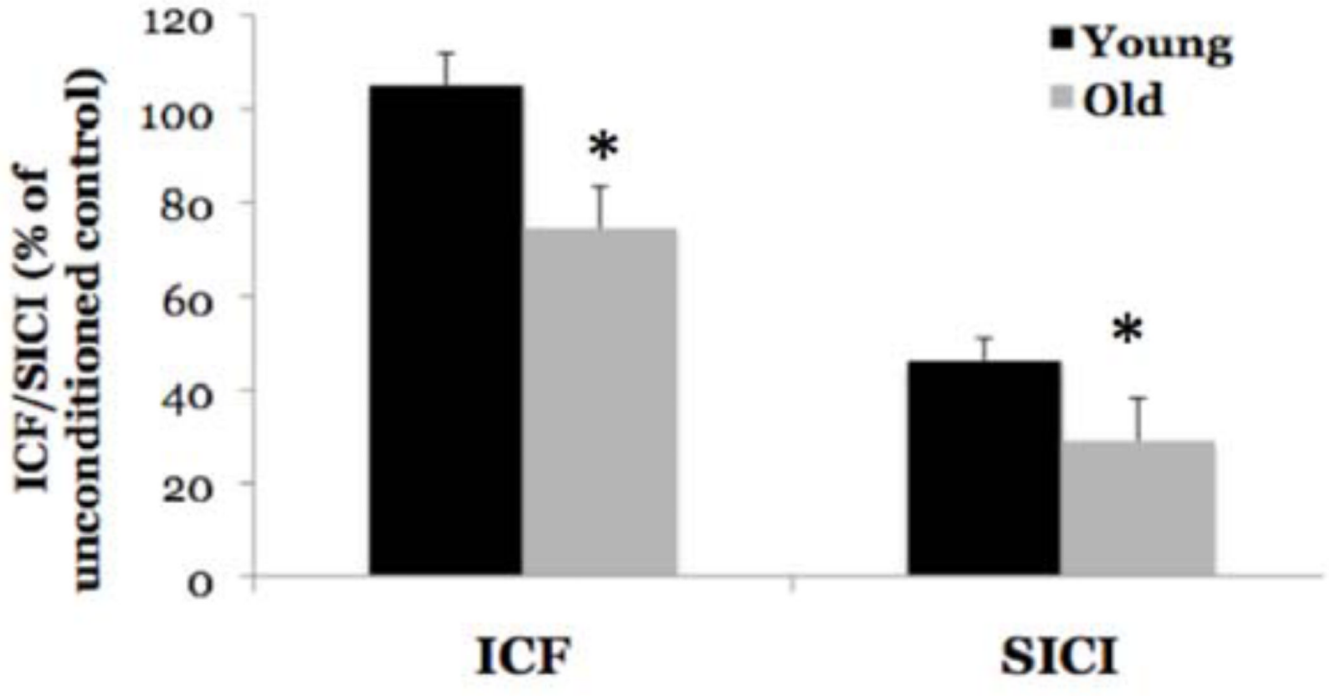

Fig. (2). Age-related changes in motor cortex excitability as assessed using paired-pulse transcranial magnetic stimulation

Older adults (70.9±1.8 yrs) exhibited less intracortical facilitation than younger adults, and more short-interval intracortical inhibition under resting conditions when compared to younger adults (21.4±0.8 yr) (*P<0.05).

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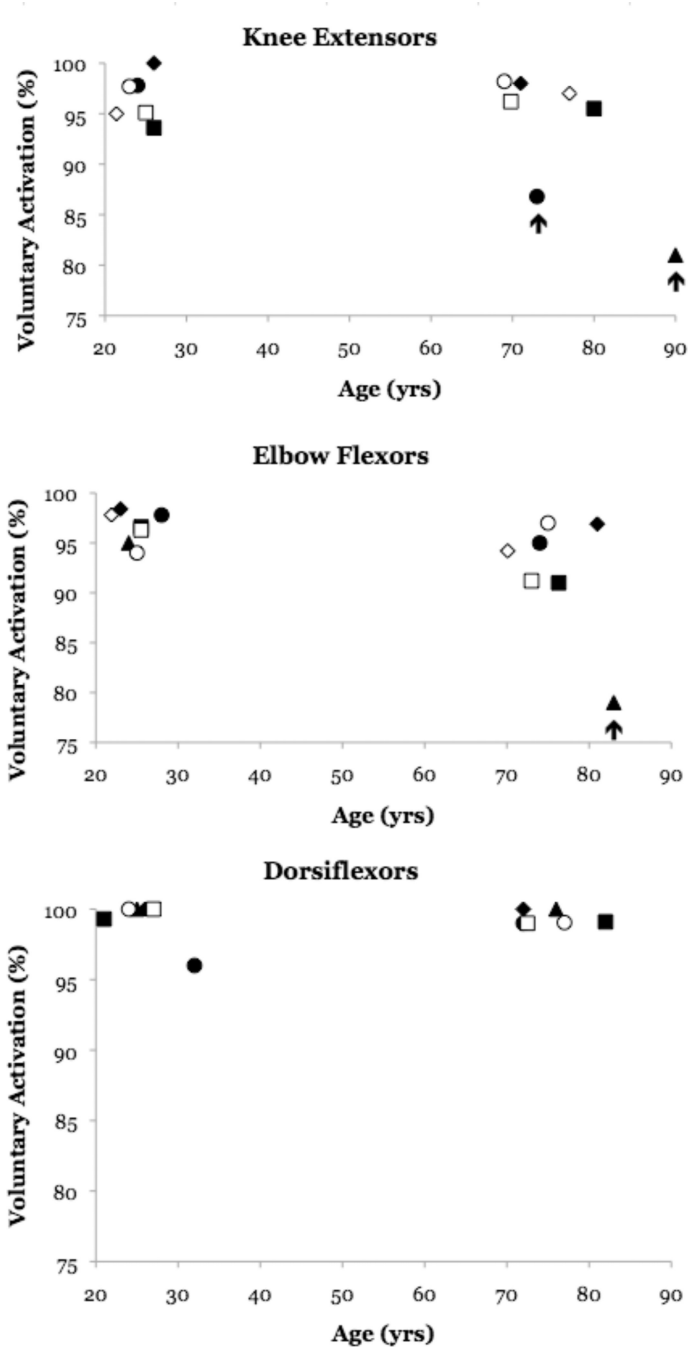

Fig. (3). Age-related changes in voluntary activation (a measure of how much of a muscle's possible force is produced by a voluntary contraction) is muscle group specific

Studies quantifying age-related differences in voluntary activation of the knee extensors (**A**), elbow flexors (**B**), and ankle dorsiflexors (**C**) during isometric contractions. Selected studies have been highlighted with an arrow pointing to them (see main text for further discussion on these specific papers).

Data points in A correspond to the following articles: Filled circles: Stevens *et al*. 2003, Filled squares: Roos *et al*. 1999, Filled diamonds: Callahan *et al*. 2009, Filled triangle: Harridge *et al*. 1999, Open circles: Wilder and Cannon 2009, Open Squares: Cannon *et al*. 2007, Open diamonds: Knight and Kamen 2001.**Data points in B correspond to the**

following articles: Filled circles: DeSerres and Enoka 1998, Filled squares: Bilodeau *et al*. 2001, Filled diamonds: Klein *et al*. 2001, Filled triangle: Jakobi and Rice 2002, Open circles: Yue *et al*. 1999, Open Squares: Hunter *et al*. 2008, Open diamonds: Yoon *et al*. 2007.**Data points in C correspond to the following articles:** Filled circles: Kent-Braun and Ng 1999, Filled squares: Conley *et al*. 1999,Filled diamonds: Lanza *et al*. 2004, Filled triangle: Klass *et al*. 2005, Open circles: Simoneau *et al*. 2005, Open Squares: Chung *et al*. 2007.