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Corticospinal and intracortical excitability of the quadriceps in active older and younger healthy adults

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ABSTRACT

Age-related declines in neuromuscular function are well-documented, though the mechanisms underlying these deficits are unclear. Specific changes in corticospinal and intracortical neurophysiology may contribute, but have not been well studied, especially in lower extremity muscles. Furthermore, variations in physical activity levels may potentially confound the interpretation of neurophysiologic findings. Therefore, the purpose of this study was to quantify differences in transcranial magnetic stimulation (TMS) measures of corticospinal and intracortical excitability of the quadriceps between healthy, active older and younger adults. Twenty younger (age: 25.2 ± 2.4 years; body mass index [BMI]: 22.1 ± 3.0 kg/m^2; 11 males and 9 females) and twenty older (age: 67.7 ± 5.5 years; BMI: 26.8 ± 3.8 kg/m^2; 11 males and 9 females) subjects who exercised regularly (at least 30 min, 3 times/week) completed testing. Motor evoked potentials (MEPs) were measured by superficial electromyographic recordings of the vastus lateralis (VL). Measures of corticospinal excitability using a double cone TMS coil included resting motor thresholds (RMT), resting recruitment curves (RRCs) and silent periods (SP). Intracortical excitability was measured using paired pulse paradigms for short interval intracortical inhibition (SICI) and intracortical facilitation (ICF). No statistically significant differences between older and younger adults were found for RMT, RRC slopes, SP, SICI or ICF measures ($p > 0.05$). The physically active nature of the older adults included in this study may have contributed to the lack of differences in corticospinal and intracortical excitability since physical activity in older adults attenuates age-related declines in neuromuscular function.

1. Introduction

Aging is associated with a number of physiological and neuromuscular changes that have been well described (Booth, Weeden, & Tseng, 1994; Brooks & Faulkner, 1994). In particular, aging is related to impaired neuromuscular function as demonstrated by reduced muscle strength and motor performance (Booth et al., 1994; Brooks & Faulkner, 1994). Multifaceted age-related changes in the physiology of the human brain likely contribute to some of these motor deficits in older adults (Anderson & Rutledge, 1996; Mattson, Maudsley, & Martin, 2004; McGinley, Hoffman, Russ, Thomas, & Clark, 2010). For example, studies have found age-related alterations in neuronal architecture and dendritic density (Anderson & Rutledge, 1996) as well as changes in neurotransmitter levels (Mattson et al., 2004). In addition, a number of studies have found age-related changes in the responsiveness of spinal motoneurons (Chalmers & Knutzen, 2004; Kido, Tanaka, & Stein, 2004; Laidlaw, Bilodeau, & Enoka, 2000; Semmler, Steege, Kornatz, & Enoka, 2000), including decreased spinal excitability (Kido et al., 2004) and increased variability in motor unit discharge rate (Laidlaw et al., 2000). Whether specific changes in corticospinal and intracortical neurophysiology also contribute to the decline in motor function with increasing age is still not clear.

TMS of the human motor cortex provides information regarding the responsiveness of both corticospinal and intracortical pathways to an imposed stimulus (Rossini, Rossini, & Ferreri, 2010). This technique has been increasingly used to elucidate information about physiological changes that might account for altered neuromuscular function. TMS uniquely contributes to our understanding of human neurophysiology through its ability to transiently interrupt, stimulate or modulate cortical areas of interest (Kluger & Triggs, 2007). Single pulse TMS can be used to assess corticospinal excitability by examining the motor threshold necessary to produce MEPs, the rate of increase in MEPs with increasing levels of stimulation (recruitment curve), and SPs. These responses are mediated at both cortical and spinal levels, providing overall information regarding corticospinal function. Cortical excitability can be more specifically assessed using paired-pulse

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TMS paradigms, which utilize a conditioning stimulus and a test stimulus at different interstimulus intervals (ISI) including SICI and ICF (Ziemann, 2003; Ziemann, Lonnecker, & Paulus, 1995).

A limited number of TMS studies have characterized motor corticospinal and, more specifically, intracortical changes associated with normal aging (Kossev, Schrader, Dauper, Dengler, & Rollnik, 2002; McGinley et al., 2010; Oliviero et al., 2006; Peinemann, Lehner, Conrad, & Siebner, 2001; Pitcher, Ogston, & Miles, 2003; Sale & Semmler, 2005; Smith, Ridding, Higgins, Wittert, & Pitcher, 2009; Wassermann, 2002). Findings from these studies have been mixed, with some suggesting decreased corticospinal or intracortical excitability with increasing age (Kossev et al., 2002; McGinley et al., 2010; Oliviero et al., 2006; Sale & Semmler, 2005) and others suggesting no age-related changes (Peinemann et al., 2001; Pitcher et al., 2003; Smith et al., 2009). Possibly, variability in subject physical activity levels might help explain some of the mixed findings, since physical activity has been shown to enhance motor cortex plasticity (Cirillo, Lavender, Ridding, & Semmler, 2009) and attenuate neuromuscular deficits in older adults (Candow, Chilibeck, Abeysekara, & Zello, 2011; Clark & Fielding, 2011). Therefore, evaluating older and younger individuals with comparable physical activity levels would allow for a more accurate assessment of specific age-related changes in corticospinal or intracortical excitability. Furthermore, most TMS investigations have focused on upper extremity muscles. Yet, evaluation of differences in corticospinal and intracortical excitability of lower extremity muscles using TMS measures is clinically important because lower extremity muscle weakness, particularly in the quadriceps, has profound functional consequences, especially in older individuals. Quadriceps weakness has been associated with decreased gait speed (Brown, Sinacore, & Host, 1995), balance (Moxley Scarborough, Krebs, & Harris, 1999), stair-climbing (Mizner, Petterson, & Snyder-Mackler, 2005) and chair rising ability (Skelton, Greig, Davies, & Young, 1994), as well as an increased risk for falls (Moreland, Richardson, Goldsmith, & Clase, 2004). Therefore, the purpose of this study was to quantify differences in TMS measures of corticospinal and intracortical excitability of the quadriceps between healthy, active older and healthy, active younger adults. We hypothesized that corticospinal excitability would be reduced in older adults as measured by RMT, RRCs and SP duration. Further, we believed that intracortical excitability would be similarly reduced as measured by SICI and ICF paradigms.

2. Methods

2.1. Subjects

Younger subjects were recruited between the ages of 20 and 35. Older subjects were recruited between 60 and 80 years old. Subjects were excluded if they had a history of diabetes, cardiovascular disease, peripheral neuropathy, neurological or psychiatric disease, lower extremity orthopedic injury, knee surgery or current knee pain, or were taking medications known to alter cortical excitability. Additionally, all subjects were screened to meet the TMS safety criteria as outlined by the National Institutes of Neurological Disorders and Stroke (Wassermann, 1998). All subjects reported exercising at least 30 min per day, three days per week. We chose to target physically active older adults to compare to physically active younger adults, because this approach would better isolate age-related changes in corticospinal and intracortical excitability without the potential confounder of decreased physical activity that often accompanies increasing age. The study was approved by the university institutional review board. All subjects provided written, informed consent before participation.

2.2. Electromyography recording

Subjects were tested in a seated and reclined position with approximately 45° of hip flexion. Surface EMG of the VL muscle was collected using two, 3 cm Ag–Ag/Cl electrodes (ConMed, Utica, NY, USA) placed midway between the iliac crest and the lateral joint line of the knee. The leg with the lowest background EMG noise was utilized (left leg: $n = 12$ younger; $n = 15$ older). Ground electrodes were placed on the contralateral medial malleolus of the ankle. EMG was collected using a Biopac MP100 unit and AcqKnowledge (v3.8.1) software (Biopac Systems Inc., Goleta, CA). The EMG signal was amplified at a gain of 2000 and was filtered online with a high pass of 10 Hz and low pass of 500 Hz.

2.3. TMS

MEPs were recorded by stimulating the motor cortex contralateral to the VL being tested with a double cone coil connected to two Magstim 200^2 units joined by a BiStim^2 module (The Magstim Company, Whitland, UK). Using a posterior–anterior orientation of the double cone coil, the optimal stimulating point was found by locating the area that produced the largest and most consistent MEPs after providing stimuli to a variety of positions on a grid drawn on a lycra cap. All subsequent testing was performed over the optimal stimulating point. Stimuli were separated by at least three seconds.

The cut-off for MEP detection was calculated by first determining the peak-to-peak amplitude of the resting EMG signal. The threshold was set two standard deviations above this amplitude. The RMT was defined as the minimum stimulator intensity required to produce 4 of 8 MEPs whose peak-to-peak amplitudes exceeded this MEP threshold. Similarly, active motor threshold (AMT) was defined as the minimum stimulator intensity required to produce 4 of 8 MEPs whose peak-to-peak amplitudes were greater than the peak-to-peak amplitude plus two times the standard deviation of the EMG signal collected while the subject lifted his/her foot five centimeters off of the testing chair by extending the knee (Clark, Issac, Lane, Damron, & Hoffman, 2008; Damron, Dearth, Hoffman, & Clark, 2008; McGinley et al., 2010). The average quadriceps EMG activity for all subjects while lifting their foot as a percentage of maximal EMG activity was $20.7 \pm 2.7\%$ (mean $\pm$ standard error of the mean (SEM)). Three trials of this contraction were collected to ensure consistent contraction levels across trials.

The RRC data were collected by providing eight stimuli at 6 stimulator intensities set at 80%, 90%, 100%, 110%, 120% and 130% of RMT. Next, paired pulse measurements were used to quantify intracortical excitability using a sub-threshold conditioning stimulus (80% RMT) followed by a supra-threshold test stimulus (120% RMT) separated by either 3 ms or 15 ms ISI (Chen et al., 1998; Kujirai et al., 1993). Pulses separated by 3 ms produce an inhibitory effect on the test stimulus (SICI) and pulses separated by 15 ms produce a facilitatory effect on the test stimulus (ICF) (Chen et al., 1998; Kujirai et al., 1993). Paired pulse parameters were chosen according to well-established guidelines (Manganotti, Acler, Zanette, Smania, & Fiaschi, 2008; Zanette, Manganotti, Fiaschi, & Tamburin, 2004). Eight SICI followed by eight ICF stimuli were administered. One set of 8 control stimuli at 120% RMT followed paired pulse testing and was used to normalize data from paired pulse testing. Finally, SP was measured from EMG recordings with eight sets of TMS stimuli delivered at 120% of AMT while the subject extended his/her knee as described earlier. The SP duration was measured from MEP onset to resumption of normal EMG activity, defined as the instant when the amplitude of the post-stimulus EMG activity changed by at least the value of the mean EMG activity from knee extension $\pm$ 1 SD (Garvey, Ziemann, Becker, Barker, & Bartko, 2001).