Recovery from supraspinal fatigue is slowed in old adults after fatiguing maximal isometric contractions

Sandra K. Hunter,1 Gabrielle Todd,2,3 Jane E. Butler,2 Simon C. Gandevia,2 and Janet L. Taylor2

1Exercise Science Program, Department of Physical Therapy, Marquette University, Milwaukee, Wisconsin; 2Prince of Wales Medical Research Institute and University of New South Wales, Sydney, Australia; and 3Discipline of Physiology, School of Molecular and Biomedical Science, The University of Adelaide, Adelaide, Australia

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Hunter SK, Todd G, Butler JE, Gandevia SC, Taylor JL. Recovery from supraspinal fatigue is slowed in old adults after fatiguing maximal isometric contractions. J Appl Physiol 105: 1199–1209, 2008. First published August 7, 2008; doi:10.1152/japplphysiol.01246.2007.—This study compared the contribution of supraspinal fatigue to muscle fatigue in old and young adults. Transcranial magnetic stimulation (TMS) of motor cortex was used to assess voluntary activation during maximal voluntary contractions (MVCs) of elbow flexor muscles in 17 young adults (25.5 ± 3.6 yr; mean ± SD) and 7 old adults (73.0 ± 3.3 yr). Subjects performed a fatigue task involving six sustained MVCs (22-s duration, separated by 10 s). Young adults exhibited greater reductions in maximal voluntary torque (67 ± 15% of baseline) than the old (37 ± 6%; P < 0.001). Increments in torque (superimposed twitch) generated by TMS during sustained MVCs increased for the young and old (P < 0.001) but were larger for the old adults at the start of the sustained contractions and during recovery (P < 0.05). Voluntary activation was less for the old adults at the start of some sustained contractions and during recovery (P = 0.02). Motor-evoked potential area increased similarly with age during the fatigue task but was greater for the old adults than young during recovery. Silent period duration lengthened less for the old adults during the fatigue task. At the end of the fatigue task, peak relaxation rate of muscle fibers had declined more in the young than the old adults. The greater endurance with age is largely due to a difference in mechanisms located within the muscle. However, recovery from the fatiguing exercise is impaired for old adults because of greater supraspinal fatigue than in the young.

In addition to adaptations in the muscle, numerous age-related changes within the central nervous system, including reductions in cortex size (41), structural degradation of cortical neurons (12), reduced motor cortical excitability (37), a decline in effective connectivity between distant motor-related cortical areas (44), reduced excitability of the motoneuron pool assessed indirectly using electromyography (EMG) (45, 46), and motoneuron degeneration (33) may impair the ability of old adults to provide high levels of neural drive to the muscle. Old adults may also be predisposed to large reductions in neural drive during fatiguing contractions, which require maintenance of high neural drive.

Central fatigue describes a progressive decline in voluntary activation of the muscle during exercise, indicating impairment of force due to mechanisms in the central nervous system (15). Voluntary activation is measured with a technique known as twitch interpolation, which traditionally involves superimposing a supramaximal electrical stimulus to the motor point of a muscle during a maximal voluntary contraction (MVC). If extra force is elicited by the stimulus (i.e., a “superimposed twitch”), then the motor units were not all recruited voluntarily, or they were discharging at rates that were not high enough to produce full fusion of force (17). Thus a superimposed twitch indicates that voluntary activation of the muscle was less than maximal and that the site of failure of voluntary activation occurred in the central nervous system, at or above the level of the motor axons (15). In maximal efforts, voluntary activation in old adults is reported as reduced in some muscles compared with young (6, 49) but not in others (26, 28). Similarly, old adults experience greater central fatigue than young during fatiguing contractions of the elbow flexor muscles and quadriceps (6, 49, 59) but not of the dorsiflexor muscles (2, 32).

A component of central fatigue is supraspinal fatigue, which is attributable to suboptimal motor output from the motor cortex (15). Supraspinal fatigue is demonstrated by an exercise-related fall in voluntary activation measured with cortical stimulation. If stimulation of the motor cortex evokes an increment in force from the muscle during a maximal effort, then the site of failure of voluntary drive can be localized at or above the level of motor cortical output (16, 51, 56). It is unknown whether supraspinal fatigue changes with increased age and whether this influences the magnitude of muscle fatigue. Understanding the site and magnitude of failure will help identify the potential for neural adaptations during neuromuscular rehabilitation in old adults. Age-related changes in

Muscle fatigue is an exercise-induced decline in maximal voluntary muscle force or power, and processes both within the muscle and within the central nervous system can contribute to this decline (14, 15). Age-related changes in the muscles and/or nervous system potentially influence the magnitude of muscle fatigue of old adults during fatiguing contractions. For example, changes in the muscle mean that old adults can be less fatigable than young adults. An age-related loss of fast motor units results in a greater relative area of type I muscle fibers in old adults (8, 13) and in slower contractile properties (24, 29, 36), which are consistent with a more fatigue-resistant muscle profile compared with young adults. As a consequence, when old adults perform isometric contractions, they fatigue less than young adults even when matched for strength (6, 9, 21, 22, 32). However, old adults do not always outperform young adults, with old adults fatiguing more during dynamic contractions (2, 35).

Address for reprint requests and other correspondence: S. K. Hunter, Exercise Science Program, Dept. of Physical Therapy, Marquette University, Milwaukee, WI (e-mail: sandra.hunter@marquette.edu).

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the structure and function of the central nervous system (12, 37, 41, 44) may predispose old adults to greater supraspinal fatigue compared with young adults. Therefore, the purpose of this study was to compare supraspinal fatigue in young and old adults using transcranial magnetic stimulation (TMS) of the motor cortex during repeated sustained isometric MVCs of the elbow flexor muscles. We hypothesized that old adults would develop greater deficits in voluntary drive from the motor cortex than young adults during sustained maximal contractions and recovery and that deficits in voluntary drive would be accompanied by changes in motor cortex “excitability.” Cortical excitability was assessed by measurement of the size of the short-latency excitatory EMG response to TMS [motor-evoked potential (MEP)] and the length of the subsequent silent period.

METHODS

Seventeen young adults (22–30 yr, 9 men) and 7 old adults (67–78 yr, 5 men) volunteered to participate in the study. The results of the young adults (men vs. women) are reported elsewhere (20). Four of the young women were not used in some of the analyses because the sex of the subject will influence the magnitude of muscle fatigue (20, 23). The exclusion of the four men resulted in an equal proportion of young men (n = 9) to young women (n = 4) (69 vs. 31%), respectively) and old men to old women (71 vs. 29%). The four young women included in all data analysis for the present study did not differ in fatigue and physical characteristics from the four women who were excluded for some variables. Specifically, the data from the women excluded for some variables were used to increase the number of subjects for associations between variables and also the voluntary activation data calculated with the estimated twitch (see Data Analysis). All subjects were healthy with no known neurological or cardiovascular disease. None of the old women were taking hormone replacement therapy. All subjects were naive to the protocol. The physical activity level of each subject was assessed with a questionnaire (30) that estimated the relative kilocalorie expenditure per week. Before participation, each subject provided written informed consent. All of the experimental procedures were approved by the University of New South Wales Human Research Ethics Committee and conducted according to the Declaration of Helsinki at the Prince of Wales Medical Research Institute, Sydney, Australia.

Recordings

Subjects were seated upright in an adjustable chair with the dominant arm held firmly at the wrist (via a secure strap) in an isometric myograph (Fig. 1A). The shoulder and elbow were flexed at 90° with the forearm vertical and fully supinated. The myograph measured isometric elbow flexion torque using a linear strain gauge (XTran, Melbourne, Australia: linear to 2 kN) (1). EMG signals were recorded with surface electrodes (Ag-AgCl, 10-mm diameter) placed over the middle of the muscle belly and the tendon of biceps brachii and triceps brachii. The electrode placed over the muscle belly was approximately midway between the anterior edge of deltoid and the proximal elbow crease for biceps and approximately midway between the posterior crista of the acromion and the olecranon for triceps. EMG signals were amplified (×100–300) and band-pass filtered (16–1,000 Hz) [model CED 1902, Cambridge Electronic Design (CED), Cambridge, UK], Force (1,000 Hz) and EMG (2,000 Hz) signals were sampled with a CED 1401 computer interface and Spike2 software (CED).

Stimulation

Two forms of stimulation were used during each experiment: electrical stimulation of the brachial plexus and TMS.

Electrical stimulation of the brachial plexus. The brachial plexus was stimulated to determine the size of the maximal compound muscle action potentials (M_max) of the biceps brachii and triceps brachii muscles while the subject was at rest. Single stimuli (100-μs duration) were delivered to the brachial plexus with a cathode in the supraclavicular fossa and an anode on the acromion (model DS7AH, Digitimer, Welwyn Garden City, Hertfordshire, UK). The stimulation intensity ranged between 60 and 180 mA.

TMS. TMS were delivered via a round coil (13.5-cm outside diameter; Magstim 200, Magstim, Whitchard, UK) over the vertex to evoke MEPs in the biceps and triceps muscles during elbow flexion contractions. The direction of current flow in the coil preferentially activated the motor cortex in the hemisphere that innervated the dominant arm. Single stimuli were delivered at an intensity that produced a large MEP in the agonist biceps muscle (minimum amplitude of 50–60% of M_max) during brief MVCs of the elbow flexor muscles but only a small MEP in the antagonist triceps muscle (amplitude <15% of M_max) (57). The average stimulus intensities for the young and old groups were 66 ± 13 and 60 ± 10% of stimulator output, respectively. The intensity of stimulation was not significantly different between groups (P = 0.29).

Experimental Protocol

Each subject visited the laboratory for one experimental session to assess voluntary activation using TMS during brief and intermittent sustained MVCs of the elbow flexor muscles. The protocol comprised:

1) Measurement of M_max at rest in biceps and triceps using electrical stimulation of the brachial plexus.

2) Performance of five sets of brief (2–3 s) control contractions separated by at least 120 s of rest to minimize fatigue. Each set of contractions involved one MVC followed by a contraction at 60% MVC and one at 80% MVC. The 60 and 80% submaximal target contractions were calculated from the force obtained in the MVC performed in the same set. The target forces were displayed on a light-emitting diode visual feedback device. Within a set, the start of the contractions were separated by 5 s, and TMS was delivered during each contraction.

3) Performance of a set of six sustained (22-s) MVCs separated by 10-s intervals (Fig. 1B). After each sustained MVC, brief contractions were performed at 60 and 80% MVC. These target torques were calculated from the voluntary torque just before cessation of the previous sustained MVC. TMS was delivered at the start (after 2 s of contraction) and end (2 s before the end of contraction) of each sustained MVC. TMS was also delivered during each brief submaximal contraction. Immediately prior to the first sustained MVC, a 60 and 80% MVC were performed. The target values for these contractions were calculated from the last brief control MVC.

4) Performance of 10 sets of brief contractions to monitor recovery after the intermittent sustained MVCs. The sets of brief contractions were similar to those performed before the sustained MVCs. One set of brief contractions was performed at 15 s, 45 s, 1 min 15 s, 2 min 15 s, 3 min 15 s, 4 min 15 s, 5 min 15 s, 6 min 15 s, 8 min 15 s, and 10 min 15 s after end of the last sustained MVC.

Data Analysis

In the text and figures, the amplitude of the superimposed twitch elicited by TMS is reported as a percentage of the voluntary torque measured immediately before TMS (16, 51). The amplitude of the superimposed twitch (N·m) was also used for calculation of voluntary activation. Voluntary activation was quantified by expressing the amplitude of the superimposed twitch (elicited from TMS) as a fraction of the estimated amplitude of the response evoked by the same stimulus at rest (estimated resting twitch) (56, 57). The amplitude of the resting twitch was estimated rather than measured directly because motor cortical and spinal cord excitability increase with activity (43). Estimation of the resting twitch was achieved for each
subject by extrapolation of the linear relation between the amplitude of the superimposed twitch and voluntary torque during brief maximal and submaximal contractions (60% MVC and 80% MVC). One regression analysis was performed for each set of brief contractions. During the fatigue task, the regression was calculated using the brief 60 and 80% MVCs and the nearest cortical stimulus delivered during a sustained MVC. The $y$-intercept was taken as the estimated amplitude of the resting twitch evoked by TMS (20, 57). The amplitude of the estimated resting twitch can be accurately determined from three data points in fresh or fatigued muscle when the contractions are >50% MVC (56). Voluntary activation (%) was calculated with the formula: voluntary activation = (1 − superimposed twitch/estimated resting twitch) $\times$ 100 (56, 57). Although the regression of voluntary torque and the superimposed twitch torque evoked during the contractions was always linear during control contractions, it was nonlinear ($r < 0.9$) in one-quarter of the contraction sets during the fatigue protocol (31% during the fatigue task and 22% during recovery). This is likely due to the speed of torque recovery or occasional large triceps MEPs. For example, if recovery of the maximal torque is rapid, then the 60 and 80% MVC contractions, which are set with respect to the preceding MVC but are performed during the rapid recovery, will represent lower percentages of the actual maximal torque. Thus the superimposed twitches on these submaximal contractions will be higher than that expected for a 60 or 80% MVC task. In these cases, nonlinear regressions and the subsequent estimations of voluntary activation and the estimated resting twitch amplitude were excluded from the statistical analysis. We excluded estimates of the resting twitch during the fatiguing contraction due to low subject numbers because poor estimates of the resting twitch were concentrated during the fatiguing contractions. Where voluntary activation is reported, the additional women were included in the analysis because this variable is not influenced by the sex of the subject (20). Other data points were excluded for young and old adults at different time points when the regression of the estimated resting twitch was $r < 0.9$.

The contractile properties of elbow flexor muscle fibers were also assessed. The amplitude of the estimated resting twitch was used as an index of the force-generating capacity of the elbow flexor muscles. The fall of torque during the period of EMG silence after a cortical stimulus was used to determine the peak relaxation rate of elbow flexor muscle fibers (53, 55). The peak relaxation rate of muscle fibers
was calculated during each MVC by measurement of the steepest rate of torque decline during the period of EMG silence immediately following TMS. This was determined as the highest negative derivative of the torque for an interval of 10 ms between two cursors placed either side of the fall in torque during the silent period. The steepest rate of torque decline was normalized to the total torque (MVC plus superimposed twitch) before the silent period. The peak relaxation rate was not included for two of the young subjects (1 man and 1 woman) because their silent periods were too brief (<100 ms).

The amplitude and area of MEPs and M_max were measured between two cursors placed at the start and end of the waveform for the biceps and triceps muscles. Because amplitude and area showed similar changes, only area is reported. M_max was only elicited at rest at the start of the experiment. The area of each MEP was normalized to the area of M_max. The silent period was measured as the interval from the stimulus to the resumption of continuous EMG. Voluntary torque was quantified by calculation of the mean torque over a 100-ms period immediately before TMS at the start and end of each sustained fatiguing contraction, during control and recovery MVCs, and during the submaximal contractions at 60 and 80% MVC.

Statistical Analysis

Data are reported as means ± SD within the text and displayed as means ± SE in the figures. Two-way, repeated-measures ANOVAs were used to compare several variables for the young and old across time. Separate ANOVAs were used for the control trials, the fatiguing contractions, and recovery. The variables included voluntary torque, percent decline in MVC torque, superimposed twitch torque, voluntary activation, and estimated resting twitch amplitude (controls only), MEP area, silent period duration, and peak relaxation rate of muscle fibers. Repeated-measures ANOVAs with age as a factor were also used to determine whether variables had returned to control values by the end of recovery. Post hoc analysis (Tukey) was used to test for differences within the ANOVAs when appropriate. Independent t-tests were used to compare young and old adults for the physical characteristics, physical activity levels, the SD in voluntary activation across the five MVC control trials (measure of variability), amplitude and area of M_max, and voluntary activation and estimated twitch amplitude during recovery. The associations between various variables are reported as the squared Pearson product-moment correlation coefficient (r^2). A significance level of P < 0.05 was used to identify statistical significance.

RESULTS

The young (25.5 ± 3.6 yr) and old adults (73.0 ± 3.3 yr) were similar in height (170 ± 8 vs. 170 ± 9 cm, respectively; P = 0.92), weight (67.8 ± 12.4 vs. 72.9 ± 12.1 kg; P = 0.41) and estimated physical activity levels (24.6 ± 18.1 metabolic equivalents·h/wk vs. 29.1 ± 31.7 metabolic equivalents·h/wk; P = 0.70).

Torque and Voluntary Activation

Brief control contractions. The young adults were stronger (66.9 ± 16.1 N·m) than old adults (48.8 ± 12.7 N·m; age effect, P = 0.02) during brief control MVCs. Voluntary torque was similar across the five MVCs for the young and old adults (time effect, P = 0.70) with no interaction of trial and age (P = 0.38). Voluntary activation during these contractions was more variable (comparison of SDs across the 5 trials for each subject) among the old than the young adults (Fig. 2A; P = 0.028). There was an age difference in voluntary activation during the control trials (P = 0.02) and an interaction of age by trial (P = 0.01; Fig. 2B). The mean voluntary activation was similar between the five trials for the young adults but increased between trials 1 and 5 for the old adults. Voluntary activation was greater for the young adults compared with the old adults in trials 1, 2, and 3 (P < 0.001) but similar for trials 4 and 5 (P = 0.13).

Fatigue. Voluntary torque declined for the young and old adults during the six sustained 22-s MVCs (time effect, P < 0.001). By the end of the sixth sustained MVC, the young adults declined to a lower torque (24.5 ± 4.6 N·m) than the old adults (31.9 ± 8.6 N·m, P < 0.001; Fig. 3A). The absolute decline in voluntary torque was greater in young adults (38.5 ± 11.9 N·m) than old adults (14.7 ± 7.4 N·m; P < 0.001). At the end of the sixth sustained MVC, voluntary torque was 37 ± 6% of the initial control MVC for the young adults and 67 ± 15% for the old adults (interaction of time and age, P < 0.001; Fig. 3B). In the recovery period, voluntary torque during brief MVCs increased toward baseline values for both the young and old adults (time effect, P < 0.001). However, young adults increased their voluntary torque (absolute and relative) at a greater rate than old adults (interaction of time and age, P < 0.001). After 10 min of recovery, both young and old adults had still not regained baseline values and were at similar percentages of their initial control MVCs (80 ± 10% for young vs. 86 ± 6% for old) (Fig. 3B). There was an association between baseline maximal voluntary torque (mean of 5 brief
reductions in torque than the old adults during the intermittent fatiguing brief control MVCs. The young adults had greater absolute and relative voluntary torque throughout the protocol is normalized to the mean of the 5 SE) is expressed as a percentage of that before fatigue. For each subject, end of the 6th sustained MVC. A linear relation is shown (r
control MVCs is plotted against the relative decline in maximal torque by the of the 10 min recovery.

22-s MVC, and during brief MVCs at the start (15 s after fatigue task) and end of each sustained control trials (mean of 5 brief MVCs), at the start and end of each sustained MVCs for the young (age effect, P = 0.17). However, there was an apparent age difference in the development of fatigue within each contraction. When the superimposed twitches evoked at the start of each sustained MVC were analyzed separately (repeated-measures ANOVA), they were bigger in old adults than young adults (5.5 ± 3.0 vs. 3.6 ± 2.3% respectively; age effect, P = 0.02). The larger superimposed twitch at the start of the sustained MVC for the old adults was specific to the first, fifth, and sixth sustained MVCs (6.0 ± 3.7 vs. 3.4 ± 2.3% for 3 contractions pooled). The superimposed twitch amplitude increased to similar levels in the old and young adults by the end of each sustained MVC (8.2 ± 3.9 vs. 7.1 ± 4.4%, respectively; age effect, P = 0.45). During recovery, the superimposed twitch of the old adults was larger than the young adults (age effect, P = 0.003; Fig. 4). By the end of recovery (last contraction) the superimposed twitches of the young and old adults were not completely returned to control values (difference between control and last contraction: P = 0.01).

During recovery, the young adults had higher voluntary activation levels than the old adults (means of all recovery: 84.2 ± 11.3 vs. 76.4 ± 13.9%, respectively; P = 0.026). At the end of recovery (last contraction), voluntary activation was still reduced compared with control values for the young and old adults (87.0 ± 9.9 vs. 86.2 ± 9.6%; respectively; effect of time, P = 0.007), and there was no interaction of time and age (P = 0.83).

Associations between fatigue and supraspinal fatigue. There was a significant association between the decline in MVC torque (fatigue) and the increase in the superimposed twitch amplitude of the SIT is expressed relative to maximal voluntary torque and is shown for the mean of the 5 brief control MVCs (control), for the start and end MVCs for the young (Fig. 4) and old adults (Fig. 4) and old adults (E: for the groups, maximal voluntary torque (means ± SE) were plotted for the mean of all recoveries: 3.9 vs. 3.7, respectively; age effect, P = 0.17). However, there was no interaction of age and time (P = 0.45). During recovery, the superimposed twitch amplitude was smaller compared with control values for the young and old adults (75.0 ± 9.9 vs. 86.2 ± 9.6%, respectively; age effect, P = 0.026). At the end of recovery (last contraction), voluntary activation was still reduced compared with control values for the young and old adults (87.0 ± 9.9 vs. 86.2 ± 9.6%; respectively; effect of time, P = 0.007), and there was no interaction of time and age (P = 0.83).

Fig. 3. Maximal voluntary torque before, during, and after the fatiguing task for the young (n = 13; ●) and old adults (n = 7; ○). A: for the groups, maximal voluntary torque (means ± SE) is expressed in N·m and is shown for the control trials (mean of 5 brief MVCs), at the start and end of each sustained 22-s MVC, and during brief MVCs at the start (15 s after fatigue task) and end of the 10 min recovery. B: for the groups, maximal voluntary torque (means ± SE) is expressed as a percentage of that before fatigue. For each subject, voluntary torque throughout the protocol is normalized to the mean of the 5 brief control MVCs. The young adults had greater absolute and relative reductions in torque than the old adults during the intermittent fatiguing contractions. C: for each subject, mean voluntary torque during the brief control MVCs is plotted against the relative decline in maximal torque by the end of the 6th sustained MVC. A linear relation is shown (r² = 0.40, y = 0.56x + 20; P < 0.05). Overall, stronger individuals experienced greater muscle fatigue (see text for further detail).

control MVCs) and the relative decline in voluntary torque at the end of the sixth sustained MVC. The fatigue was related to the initial absolute maximal torque such that stronger individuals exhibited greater fatigue (r = 0.63, r² = 0.40, P < 0.01; n = 24; Fig. 3C). When the age groups were considered separately, the relationship was significant for the young adults (r = 0.79, r² = 0.63, P < 0.001; n = 17) but not the old adults (r = 0.41, r² = 0.17, P = 0.35; n = 7).

Voluntary activation and fatigue. The increments in torque (superimposed twitch) generated by TMS, and expressed relative to the voluntary torque just before the stimulus, increased during the sustained MVCs for the young and old adults (time effect, P < 0.001) but returned toward baseline values during the recovery period (time effect, P < 0.001). The amplitude of the superimposed twitch was similar for young and old adults during sustained MVCs (age effect, P = 0.17). However, there was an apparent age difference in the development of fatigue within each contraction. When the superimposed twitches evoked at the start of each sustained MVC were analyzed separately (repeated-measures ANOVA), they were bigger in old adults than young adults (5.5 ± 3.0 vs. 3.6 ± 2.3% respectively; age effect, P = 0.02). The larger superimposed twitch at the start of the sustained MVC for the old adults was specific to the first, fifth, and sixth sustained MVCs (6.0 ± 3.7 vs. 3.4 ± 2.3% for 3 contractions pooled). The superimposed twitch amplitude increased to similar levels in the old and young adults by the end of each sustained MVC (8.2 ± 3.9 vs. 7.1 ± 4.4%, respectively; age effect, P = 0.45). During recovery, the superimposed twitch of the old adults was larger than the young adults (age effect, P = 0.003; Fig. 4). By the end of recovery (last contraction) the superimposed twitches of the young and old adults were not completely returned to control values (difference between control and last contraction: P = 0.01).

During recovery, the young adults had higher voluntary activation levels than the old adults (means of all recovery: 84.2 ± 11.3 vs. 76.4 ± 13.9%, respectively; P = 0.026). At the end of recovery (last contraction), voluntary activation was still reduced compared with control values for the young and old adults (87.0 ± 9.9 vs. 86.2 ± 9.6%; respectively; effect of time, P = 0.007), and there was no interaction of time and age (P = 0.83).

Fig. 4. Superimposed twitch (SIT) evoked by cortical stimulation during MVCs for the young (●) and old adults (○). Group means (SE) are plotted for the mean of the 5 brief control MVCs (control), for the start and end of each sustained MVC (fatigue), and for the brief MVCs during recovery. The amplitude of the SIT is expressed relative to maximal voluntary torque measured immediately before stimulation. There was no age difference at the end of each sustained contraction during the fatiguing task (P > 0.05). However, at the start of the sustained contractions and during recovery the old adults had a greater superimposed twitch amplitude (P < 0.05) than young adults.
throughout the fatiguing task ($r = -0.44$, $r^2 = 0.19$, $P < 0.001; n = 264$). Those subjects who had the greatest relative decline in MVC torque (fatigue) showed the greatest enlargement in the superimposed twitch. This association was stronger in the old adults ($r = -0.69$, $r^2 = 0.47$, $P < 0.001$, $n = 77$) compared with the young adults ($r = -0.43$, $r^2 = 0.19$, $P < 0.001; n = 187$).

During recovery there was also a significant relationship between the change in MVC torque and the change in the superimposed twitch ($r = -0.36$, $r^2 = 0.13$, $P < 0.001$, $n = 264$). Those subjects who had the greatest change (recovery and improvement) of MVC torque also had the greatest change (reduction and improvement) in the superimposed twitch. Similarly, this relationship was stronger in the old adults ($r = -0.50$, $P < 0.001$, $r^2 = 0.25; n = 77$) compared with the young adults ($r = -0.14$, $r^2 = 0.02$, $P = 0.05; n = 187$).

**MEPs and Silent Period**

The average amplitude and area of the resting biceps $M_{max}$ were larger for the young compared with the old adults (21.2 ± 3.7 mV vs. 15.0 ± 2.9 mV, $P = 0.002$, and 175 ± 34 vs. 112 ± 29 mV·ms, $P = 0.005$, respectively). The resting triceps $M_{max}$ was also larger for the young adults (amplitude, 13.2 ± 3.8 mV) than the old adults (7.8 ± 3.7 mV, $P = 0.006$).

**Brief control contractions.** MEPS in biceps differed in size with the strength of brief contractions. Larger MEPS were evoked during the 60 and 80% MVCs, whereas MEPS were smallest during MVCs. In the 60, 80, and 100% MVCs, MEP areas for the young adults were 76 ± 17, 78 ± 15, and 52 ± 13% $M_{max}$ and for the old adults, 80 ± 13, 71 ± 14, and 59 ± 10% $M_{max}$, respectively. Although there was no main effect of age ($P = 0.53$) for MEP area, there was an interaction between contraction intensity and age ($P < 0.01$) because the largest MEP was during the 80% MVC for the young adults and during the 60% MVC for the old adults. There was also no difference between the young adults and old adults for the area of the small MEP in triceps elicited during the submaximal contractions and MVC (9.2 ± 5.4 vs. 11.6 ± 7.0% $M_{max}$). In biceps, the duration of the silent period following cortical stimulation during brief control MVCs was similar for the young (149 ± 64 ms) and old adults (142 ± 40 ms, $P = 0.82$; Fig. 6).

**Fatigue and recovery.** The area of the MEP in biceps increased (time effect, $P < 0.001$) similarly during the sustained MVCs for both the young and old adults (age effect, $P = 0.62$; Fig. 5A) with no interaction of age and time ($P = 0.41$). MEP area increased from 58 ± 11% $M_{max}$ at the start of the first sustained MVC to 118 ± 31% $M_{max}$ at the end of the sixth sustained MVC for the young adults and from 67 ± 13 to 93 ± 26% $M_{max}$ for the old adults. During recovery, there was a main effect of age on MEP area ($P = 0.03$). Old adults had a larger MEP area than the young adults. MEP area decreased (time effect, $P < 0.01$) at a similar rate for the young and old adults toward control values during the 10 min of recovery. Both young and old adults in the MEP area had returned to control values after 10 min recovery (time effect, $P = 0.20$) so that there was no difference between control and the last contraction in recovery, with no interaction of age and time ($P = 0.16$). However, there remained an age difference ($P = 0.02$).

Because MEP size is greater at submaximal intensities of contraction (34, 56), we determined the association between the MEP and a measure of voluntary activation to help understand the larger MEP size for the old than the young adults during recovery. During recovery, there was an association between the MEP area and the amplitude of the superimposed twitch. The MEP area was related with a quadratic trend to the amplitude of the superimposed twitch ($r = 0.58$, $r^2 = 0.33$, $P < 0.001$) (Fig. 5B) such that individuals with a greater superimposed twitch amplitude (i.e., lower voluntary activation) had a greater MEP area. This association was stronger in the young adults ($r = 0.55$, $r^2 = 0.30$, $P < 0.001$) than the old adults ($r = 0.38$, $r^2 = 0.15$, $P < 0.001$).

The duration of the silent period in biceps increased from the start to the end of the fatigue task and during each of the 22-s sustained MVCs ($P < 0.001$; Fig. 6). The overall increase in silent period duration showed a quadratic trend (time effect, $P = 0.037$). There was an interaction of time and age for this trend ($P = 0.034$) because the increase in the silent period duration was less for the old adults than the young adults during the fatiguing task. The silent period duration decreased toward baseline during recovery MVCs (time effect, $P < 0.01$) but was similar for the two groups (age effect, $P = 0.90$). Direct comparison of the last recovery MVC showed that its
silent period had fully recovered and was even briefer in duration than control contractions for both young and old adults (P = 0.01).

Muscle Properties

Estimated resting twitch amplitude. The amplitude of the baseline estimated resting twitch was similar for the young (14.6 ± 7.6 N·m; n = 13) and old adults (13.2 ± 4.2 N·m; n = 7; age effect, P = 0.30). In some subjects, the estimated resting twitch could not be calculated during the fatiguing protocol, and so these data are not reported (see METHODS). Resting twitch amplitude was similar for absolute values of the young and old adults during recovery (data pooled) (6.8 ± 2.4 vs. 7.4 ± 2.9 N·m, respectively; age effect, P = 0.14), but the relative difference from control was more for the young than the old adults (52 ± 17 vs. 44 ± 21%, respectively; age effect, P < 0.01). Values were still depressed after 10 min of recovery compared with control values for both young and old adults (44 ± 17 vs. 37 ± 25% difference from control).

Peak relaxation rate of muscle fibers. The peak relaxation rate (measured during the TMS-induced silent period) was greater for the young (–12.9 ± 2.4 s⁻¹, n = 11) than the old adults (–8.2 ± 3.2 s⁻¹, n = 7, age effect, P < 0.01) in the control trials, fatigue task (age effect, P = 0.015), and recovery (age effect, P < 0.001; Fig. 7A). That is, the muscle of the young adults relaxed more quickly than that of the old adults. During the fatigue task, the peak relaxation rate declined for both age groups during the first two sustained MVCs and then remained stable thereafter (quadratic trend; P < 0.001; Fig. 7B). There was a significant interaction of age and fatigue (P = 0.03) because old adults had a smaller decline in peak relaxation rate than the young adults during the fatigue task. The relative change in peak relaxation rate from control values was 52 ± 24% for the young adults and 45 ± 23% for the old adults. Both the young and old adults had recovered to initial control values after 10 min of recovery.

There was an association between the initial peak rate of relaxation and the relative decline in voluntary torque at the end of the sixth sustained MVC (Fig. 7B) such that individuals whose muscles relaxed more quickly exhibited greater fatigue (r = 0.76, r² = 0.58, n = 22, P < 0.001). This association for the young was r = 0.69, r² = 0.48 (n = 15, P < 0.01) and r = 0.66, r² = 0.44 (n = 7, P = 0.05) for the old adults.

Furthermore, the change in peak rate of relaxation was associated with the relative decline in voluntary torque at the end of the sixth sustained MVC (r = 0.40, r² = 0.25; n = 22; P < 0.01). This association between slowing of relaxation and decrease in voluntary torque was similar throughout the fatiguing protocol. That is, the change in peak rate of relaxation was correlated with the relative decline in voluntary torque at the end of the each of the sustained MVCs (r = 0.51, r² = 0.26; n = 132; P < 0.001). This association was significant for both the young (r = 0.45, r² = 0.20; n = 90; P < 0.001) and old adults (r = 0.54, r² = 0.29; n = 42; P < 0.001).
DISCUSSION

This study used motor cortical stimulation to compare the magnitude of supraspinal fatigue during intermittent sustained isometric MVCs of the elbow flexor muscles in young and old adults. Both groups of subjects had similar physical activity levels, and all subjects were naive to the testing protocol. The new findings were that voluntary activation measured using cortical stimulation decreased similarly for young and old adults during sustained MVCs, but recovery from this central fatigue occurred more slowly in the older adults. The slower recovery from central fatigue experienced by old adults was due to processes occurring at or above the level of the motor cortical output (i.e., supraspinal fatigue). The EMG response to cortical stimulation also differed between young and old adults: 1) MEP size increased similarly during the sustained contractions with age but was greater during recovery for the old than the young adults and this was associated with voluntary activation levels; and 2) silent period duration increased with fatigue, but this was less for the old than the young adults. Last, age differences in the contractile properties of the muscle indicate that reduced fatigue in the old adults during performance of the isometric fatiguing task was due to mechanisms in the muscle.

Muscle Fibers of Old Adults Are Less Fatigable Than Young Adults

The young adults were stronger than the old adults, but the reduction in maximal voluntary torque during the fatiguing task was less for the old adults. These findings are consistent with other studies that have observed greater fatigue resistance for old adults compared with young adults during isometric contractions (6, 9, 21, 22, 32). The stronger subjects experienced greater fatigue especially within the young adults (Fig. 3C). Strength therefore can only partially explain the age difference in fatigue and only among the young adults because 1) the relationship between strength and fatigue was significant among the young adults but not the old adults, as observed previously (21), and 2) even when matched for strength, healthy old adults exhibit greater endurance than young adults (9, 22).

For both groups of subjects, both peripheral and supraspinal mechanisms contributed to the muscle fatigue observed during sustained MVCs and in the recovery period. Comparison of the amplitude of the estimated resting twitch for the young and old adults in the recovery period showed that the fatiguing protocol resulted in a greater relative reduction in the twitch for the young adults. This suggests that the effect of age on muscle fatigue may be largely explained by processes within the muscle. During the fatigue task, the peak relaxation rate of muscle fibers declined more for the young than the old adults, whereas before fatigue, the old adults had slower relaxation rates. Thus subjects who initially had a faster peak rate of muscle relaxation exhibited greater muscle fatigue. This was true for the young and old adults so that the initial peak rate of muscle relaxation explained 48% of the variance in the decline in torque for the young and 44% for the old adults. Accordingly, a change in peak rate of relaxation was associated with a change in MVC torque during the fatigue task and recovery. These results are consistent with a different proportional area of fiber types in the elbow flexors for the two age groups. Typically, old adults have a greater proportion of type I area than young adults in the bicep brachii (29, 36) and therefore a more fatigue-resistant muscle. This changed proportion results from the age-related loss of type II motor units and selective reduction in type II fiber size (8, 13, 24). Furthermore, the muscles of old adults have greater reliance on oxidative sources of ATP during a fatiguing contraction (27, 31). The more fatigue-resistant muscle of the old adults in our study was not confounded by any difference in physical activity levels.

Voluntary Activation Differed With Age During Recovery

Before fatigue, voluntary activation was slightly less for the old adults than the young adults during the first three brief control MVCs but was similar for the remaining two brief control MVCs (Fig. 2). Thus practice of MVCs allowed the old adults to increase motor cortical drive to the muscle. In contrast, the young adults performed consistently across all five trials. Both young and old subjects were naive to the protocol and did not undergo a familiarization session. This initial age difference in voluntary activation and the effect of practice were also observed for the elbow flexor and elbow extensor muscles when voluntary activation was measured with nerve stimulation (26). Thus old adults require more practice to achieve maximal levels of voluntary drive compared with young adults even for a simple isometric task. Furthermore, voluntary activation among the old adults was more variable than the young adults. Although voluntary activation varies among individuals (1, 54), our data suggest that the variability with age may be minimized with practice for some older people. Because old adults have slower muscle contractile properties (Fig. 7), they may require lower motor unit firing rates (10, 38) to maintain full fusion of force. This in turn suggests that old adults may require lower levels of descending drive to perform isometric contractions relatively well so that force production during isometric contraction may not be overly sensitive to impairment in output from the motor cortex.

Both young and old adults had reduced ability to produce optimal drive from the motor cortex during the sustained contractions because the size of the superimposed twitch increased during the fatiguing task. Thus the reductions in maximal torque during the fatiguing task were in part due to central fatigue at a site at or above motor cortical output. However, there was no main effect of age on the degree of supraspinal fatigue during the sustained contractions. There was the exception of reduced voluntary activation estimates in the old adults at the start of several of the sustained MVCs compared with the young (see Fig. 4). Although voluntary activation was similar for both age groups at the end of these sustained contractions, the lower voluntary activation at the start of the MVCs may have contributed to enhanced endurance with age. Association data also indicated some contribution of central fatigue during the fatiguing task to the reduction in torque, particularly for the old adults. These data indicated that 47% of the change in torque was explained by the reduction in voluntary activation for the old adults and 19% for the young adults. For both young and old adults, peripheral mechanisms must also have significantly contributed to the loss of torque as indicated by our measurements of muscular fatigue.
Consistent with their lower voluntary activation levels at the start of the repeated sustained contractions, old adults also exhibited lower voluntary activation than the young adults during the recovery period. There was a significant association between the change in MVC torque and change in voluntary activation for the old adults and a much weaker relation for the young. For the old adults, 25% of the recovery in torque was explained by the recovery in voluntary activation, and almost none was explained for the young adults (only 2%). Thus peripheral mechanisms likely contributed to most of the recovery in the young adults. However, the reduced voluntary activation contributed significantly to the slower recovery of voluntary force in the old adults. The age-related difference in voluntary activation during recovery was not explained by a difference in corticospinal excitability. The duration of the silent period during the recovery period was similar in the two age groups, and MEPs were larger for the old adults. The age-related change in voluntary activation during recovery could be a consequence of age-related changes in cortical activity for a motor task. Functional magnetic resonance imaging studies in healthy young adults also indicate that after a fatiguing contraction there is reduced activity in primary and secondary motor areas as well as the cerebellum (3, 5). Whether this pattern changes with aging is not known. In general, during nonfatiguing tasks old adults show less activity in motor cortical areas when performance is impaired (11, 18) and greater cortical activity in a wider network of brain regions to successfully execute the same motor task at the same intensity (19, 42, 58). This age-related change in pattern of cortical activity is thought to be due to compensation for ineffective cortical areas due to local structural and chemical changes in the aging brain and/or age-related impairment in intracortical inhibitory processes (42, 58). If old adults have decreased effectiveness of neural drive, then this will limit voluntary activation.

**MEP Area and Silent Period**

Changes in the MEP size were similar for the young and old adults during the control contractions and the fatiguing task. The area of MEPs elicited during the sustained contractions increased with fatigue as reported in previous studies (20, 52). The growth in the MEP size is due to an increase in cortical excitability (52), which appeared similar for the young and old adults during the sustained contractions. In contrast, MEPs were greater in old than young adults during the recovery period. Although the MEP will be influenced by the changes in the M wave during a fatiguing contraction (52), there is little evidence to suggest that the change in M wave with fatigue and recovery differs between young and old adults for isometric contractions (7, 32). For a dynamic fatiguing protocol, the M wave decreased more for the old adults than the young adults; however, the old adults fatigued more than the young (2). Thus the age-related changes in the M wave during a fatiguing task and the magnitude of fatigue are probably more strongly influenced by the type of task performed. Consequently, the larger MEPs of the old adults were probably due to the old adults activating less muscle during “maximal” efforts, as indicated by their lower levels of voluntary activation (see below). We found a significant association between MEP area and level of voluntary activation for the young and old adults (Fig. 5B). Greater variability in MEPs among the old adults probably contributed to the lower associations in the old adults compared with the young adults (40). Low voluntary activation suggests that old adults were activating fewer motoneurons and at lower firing rates. Such disfacilitation leads to larger MEPs in accordance with the relation between MEP size and the contraction intensity (34, 56).

The duration of the silent period was similar with age during control contractions but increased to a lesser extent in the old than the young adults during the sustained contraction. Old adults have been reported to have shorter duration silent periods compared with young adults, particularly during complex tasks (37, 45). The initial part of the silent period (50–100 ms) is influenced by both spinal and cortical mechanisms, but the latter part represents activity in intracortical inhibitory circuits (25). The increase in the duration of the silent period with fatigue in the present study in both young and old adults may indicate greater intracortical inhibition, or perhaps a limit to drive the primary motor cortex (4). The silent period lengthened less in the old than the young adults and may be related to age-related impairment of cortical inhibitory processes (37, 39). Because increases in the silent period are associated with maintained high levels of cortical activity (50, 51), decreased lengthening could also be consistent with lower effective motor cortical activity in the old adults despite their similar voluntary activation to the young subjects at the end of the sustained contractions.

In conclusion, muscle fatigue was less in old adults than young adults during repeated sustained maximal voluntary contractions. Old adults had greater supraspinal fatigue at the start of sustained MVCs and during the recovery period, presumably as a result of the cumulative effects of exercise on the central nervous system. The changes in the EMG responses to cortical stimulation were different for young and old adults during the fatiguing task (silent period) and recovery (MEP). These differences probably reflect consequences of age-related changes in voluntary drive during muscle fatigue rather than indicating underlying mechanisms. Peripheral fatigue was less for the old adults than the young. Muscle relaxation rates measured during the contractions suggest that this reflects a different distribution of muscle fiber types. Thus the greater fatigue resistance with age during a maximal fatiguing contraction of the elbow flexor muscles can be explained by an age difference in peripheral fatigue within muscle. However, recovery from fatiguing exercise is impaired for old adults because of continued supraspinal fatigue. Although the present study looked at isometric maximal contractions, sustained low-force contractions also causes prominent supraspinal fatigue (47, 48). Thus the slowed recovery of old adults may lead to poor muscle activation and increased feelings of effort in everyday tasks.

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