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Male human motor cortex stimulus-response characteristics are not altered by aging

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Smith AE, Sale MV, Higgins RD, Wittert GA, Pitcher JB. Male human motor cortex stimulus-response characteristics are not altered by aging. *J Appl Physiol* 110: 206–212, 2011. First published November 11, 2010; doi:10.1152/japplphysiol.00403.2010.—Evidence suggests that there are aging-related changes in corticospinal stimulus-response curve characteristics in later life. However, there is also limited evidence that these changes may only be evident in postmenopausal women and not in men. This study compared corticospinal stimulus-response curves from a group of young men [19.8 ± 1.6 yr (range 17–23 yr)] and a group of old men [n = 18, aged 64.1 ± 5.0 yr (range 55–73 yr)]. Transcranial magnetic stimulation (TMS) over the contralateral motor cortex was used to evoke motor potentials at a range of stimulus intensities in the first dorsal interosseous muscle of each hand separately. There was no effect of age group or hemisphere (i.e., left vs. right motor cortex) on motor evoked potential (MEP) amplitude or any other stimulus-response characteristic. MEP variability was strongly modulated by resting motor threshold but not by age. M-wave (but not F-wave) amplitude was reduced in old men, but expressing MEP amplitude as a ratio of M-wave amplitude did not reveal any age-related differences in cortically evoked stimulus-response characteristics. We conclude that male corticospinal stimulus-response characteristics are not altered by advancing age and that previously reported age-related changes in motor cortical excitability assessed with TMS are likely due to changes inherent in the female participants only. Future studies are warranted to fully elucidate the relationship between, and functional significance of, changes in circulating neuroactive sex hormones and motor function in later life.

Florey Adelaide Male Ageing Study; corticospinal stimulus-response curves; transcranial magnetic stimulation

MEASURES OF EXCITABILITY of single or multiple neurons are commonly used to determine the short- and long-term effects of different input stimuli on the output characteristics of neuronal activity. At the single-neuron level, excitability depends on the combined effect of a number of intrinsic membrane properties, including resting potential, input resistance, membrane capacitance, and time- and voltage-dependent conductances (19). A commonly used approach is determination of these output characteristics over the range of stimulus intensities that elicit a response from the neuron or neuronal assembly. This is termed the input-output or stimulus-response relationship.

In humans in vivo, the corticospinal stimulus-response relationship for a given muscle can be obtained by stimulating a muscle's primary motor cortical (M1) representation with increasing intensities of transcranial magnetic stimulation (TMS) and recording the motor potentials evoked in the muscle (MEPs). In hand muscles, this elicits a stimulus-response curve shape that is typically sigmoidal (3, 23). The curve provides a relatively sensitive overall measure of the excitability of the corticospinal projection, with different curve components providing more specific information. TMS activates the corticospinal tract either pre- or transynaptically, and the resting motor threshold (rMT) reflects the excitability and membrane channel characteristics of the cortico-cortical axons and their excitatory synapses with the motor cortical output neuron (reviewed in Ref. 35). Diffusion-weighted imaging has also shown that the rMT is strongly correlated with the maturation, myelination, and structural integrity of the white matter of M1 and the premotor cortex (14). However, rMT is also dictated by the excitability of the spinal motoneurons since at least part of this pool must also discharge for an MEP to be evoked in the muscle. The slope of the curve is believed to reflect the size of the cortical representation and the distribution of excitability within the corticospinal projection (31). For example, increases in the cortical map area following ischemic anesthesia have been shown to be accompanied by concomitant increases in the slope of the corticospinal stimulus-response curve (26). The area under the curve (AUC) appears to be a relatively robust overall measure of corticospinal output and projection strength (24, 34).

Several factors are known to influence the stimulus-response properties of MEPs with single-pulse TMS, such as voluntary contraction (3, 7) and training (1, 27), as well as various neurological disorders such as stroke (10), Parkinson disease (15, 18) and focal hand dystonia (25). A number of studies have reported age-related changes in the corticospinal stimulus-response curve when young adults are compared with older adults in middle to later life (22, 23, 34). Pitcher et al. (23) reported that older adults required greater stimulus intensities to reach maximal motor output in the corticospinal projection to intrinsic hand muscles. In addition, the trial-to-trial variability of responses was greater in older subjects, specifically at low, near-threshold, TMS intensities. However, their findings also indicated that the age-related changes in their sample were being driven by changes in the women in the study and not by changes in the men, although the sample size was not sufficiently large to fully elucidate this. Therefore, the purpose of the present study was to determine whether the input-output characteristics of human motor cortex are modulated by age in a larger study population of exclusively male subjects.

MATERIALS AND METHODS

Thirty-one healthy, neurologically normal male subjects gave informed written consent to participate in the study. The subjects were divided into two groups: young [n = 13; mean ± SD age = 19.8 ±

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1.6 yr (range 17–23 yr)] and old [n = 18; age 64.1 ± 5.0 yr (range 55–73 yr)]. All subjects were right handed (mean laterality quotient = 0.83) as assessed by a modified version of the Edinburgh Handedness Questionnaire (21). All investigations were ethically approved by the Royal Adelaide Hospital and the University of Adelaide Human Research Ethics Committees and were performed in accordance with the Declaration of Helsinki (1998). Older subjects were all members of the Florey Adelaide Male Ageing Study cohort (FAMAS) (16, 17), whereas younger subjects were recruited from university notice boards.

Stimulation and EMG recording. Subjects were seated comfortably in a reclining chair with both hands and forearms supported. Surface electromyographic (EMG) recordings were obtained from the first dorsal interosseous muscle (FDI) of each hand with bipolar Ag-AgCl electrodes in a belly-tendon montage. EMG signals were sampled at 5 kHz with a laboratory interface (Cambridge Electronic Design 1401, Cambridge, UK), filtered (20 Hz–1 kHz) (D360, Digitimer, Welwyn Garden City, UK) and analyzed off-line. All recordings were made with a 50-Hz notch filter because, at the time, the laboratory was temporarily located in a building with excessive 50-Hz environmental noise. This is evident in the MEP traces illustrated in Fig. 1 as a characteristic wavelet complex immediately after the MEP.

Transcranial magnetic stimulation. Single-pulse TMS was applied through a figure-of-eight coil (outer diameter of each wing 90 mm) that was connected to a Magstim 200 magnetic stimulator (Magstim, Whitland, UK). The coil was held tangentially to the skull, with the handle pointing posteriorly and laterally at an angle of 45° to the sagittal plane, at the optimal scalp site to evoke a MEP in the relaxed FDI of the target hand. This coil orientation induces current flowing posterior to anterior in the underlying cortical tissue in a plane perpendicular to the estimated alignment of the central sulcus. The rMT was defined as the lowest stimulator output at which 5 MEPs with a minimum peak-to-peak amplitude of 50 μV were evoked from the resting FDI in 10 consecutive trials.

Stimulus-response curve protocol. A stimulus-response curve for the MEP amplitude evoked in the resting FDI by TMS was constructed for both hemispheres of motor cortex with the protocol previously described by Pitcher et al. (23). The order in which the hemispheres were assessed was randomized between subjects. Ten stimuli were delivered at each intensity, beginning 10% below rMT and increasing incrementally in 5% steps either to 100% of stimulator output or to a stimulus intensity at which MEP amplitude had reached a plateau. The peak-to-peak amplitude of each MEP was measured and the average of the 10 amplitudes calculated. The amplitudes of the MEP averages were plotted against stimulus intensity for each hemisphere. The Marquardt-Levenberg algorithm for least-squares convergence (Sigmaplot for Windows 10.0, Systat) was used to calculate the best fit of the cortical stimulus-response curves of each subject, and resulted in either four- or five-parameter sigmoidal curves (see Ref. 23). Several further curve characteristics were derived from the equations for the four- and five-parameter sigmoids including the predicted resting threshold (prMT), slope of the curve at 10% of maximum stimulus intensity ($slope_{10\%}$), slope of the curve at 25% of maximum stimulus intensity ($slope_{25\%}$), and maximum slope ($slope_{max}$) (see Ref. 23 for equations). AUC was calculated with Sigmaplot software (v.9.0, 2004 Systat Software) with the algorithm $yi(xi + 1 - xi) + (1/2)(yi + 1 - yi)(xi + 1 - xi)$, where y is the stimulus intensity and x is the MEP amplitude at a given intensity.

The maximum MEP amplitude (MEP_{max}) was the largest peak-to-peak, ensemble-averaged MEP amplitude recorded. The coefficient of variation (CV) of MEP amplitude was also calculated for each set of 10 MEPs at each intensity (i.e., standard deviation divided by the mean MEP amplitude).

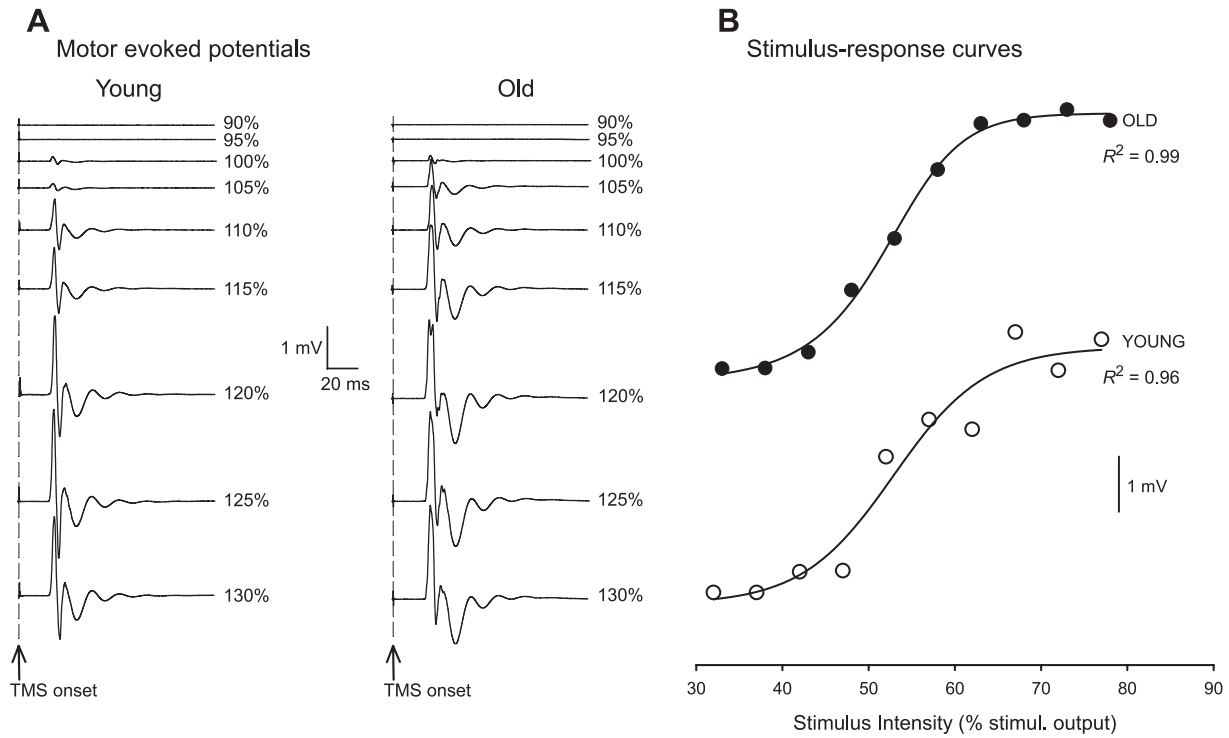

Fig. 1. The stimulus-response relationship for resting first dorsal interosseous muscle (FDI) in 1 representative young and 1 representative old subject with similar resting motor thresholds (rMTs). *A*: average motor evoked potentials (MEPs) (n = 10) recorded over a range of transcranial magnetic stimulation (TMS) intensities expressed as % rMT. Vertical dashed line indicates when the TMS was delivered. Amplitude of MEPs increased progressively with increasing stimulus intensity and reached a plateau at ~120% rMT in both young and old subjects. The post-MEP wavelet complex evident in each trace is characteristic of 50-Hz notch filtering. *B*: stimulus-response curve obtained for both subjects from the averaged peak-to-peak amplitudes of the MEPs obtained at each stimulus intensity (i.e., illustrated in *A*). Both curves were fitted with a 5-parameter sigmoid [R^2 = 0.99 (old) and 0.96 (young)].

Spinal excitability and M waves. In 20 subjects (7 young, 13 old), 10 consecutive single, supramaximal stimuli were applied transcutaneously over the ulnar nerve at the wrist with a constant-current peripheral nerve stimulator (DS7A, Digitimer) and the maximal M waves evoked at 4-s intervals were recorded from the right FDI (20 Hz–1 kHz, gain ×300). Pulse width was 100 μs at 250 V, and the current was adjusted individually to evoke a supramaximal M wave. The mean MEP amplitude-to-M wave ratio at each stimulus intensity was calculated for the right hand, and young and old subjects were compared.

One trial of 20 consecutive F waves was also similarly evoked and recorded from FDI (100 Hz–1 kHz, gain ×1,000). F waves were analyzed for maximum amplitude, chronodispersion (difference in latency between the longest- and shortest-latency F waves recorded), and persistence (number of definable F waves recorded in 20 consecutive stimuli). The maximum F-wave amplitude was expressed as a ratio of the maximum M wave.

Statistical analysis. The FDI MEP data [mean MEP amplitude, MEP-to-M wave ratio (right hand only), and CV of MEP amplitude at each intensity] were analyzed with repeated-measures analyses of variance (ANOVA) with within-subject factors hemisphere (up to 2 levels: left and right) and intensity (up to 9 levels: 90% rMT, 95% rMT, 100% rMT, 105% rMT, 110% rMT, 115% rMT, 120% rMT, 125% rMT, 130% rMT) and between-subject factor age group (up to 2 levels: young and old).

Separate repeated-measures ANOVA (SPSS Statistics v.17.0, SPSS, 2009) were undertaken for rMT, prMT, $slope_{10\%}$, $slope_{25\%}$, $slope_{max}$, MEP_{max}, and AUC, with the within-subject factor hemisphere (up to 2 levels: left and right) and the between-subject factor age (up to 2 levels: young and old).

Post hoc analyses were performed where appropriate with Bonferroni's comparison with corrections. Statistical significance was assumed at an α-level of $P \leq 0.05$. Data are expressed as means ± SD unless otherwise indicated. Stimulus intensity is expressed as a percentage of maximum stimulator output unless otherwise indicated.

RESULTS

No participants reported any adverse effects during or after the study. Of the 31 subject curves obtained, 25 (7 young, 18 old) were best fitted by a five-parameter sigmoid and the remaining 6 by a four-parameter sigmoid curve (5 young, 1 old). A representative example of one young and one old subject is shown in Fig. 1.

Resting motor threshold. There was no difference in rMT when hemispheres were compared ($F_{1,28} = 0.14$) or between the age groups ($F_{1,28} = 0.35$) and no hemisphere × age interaction ($F_{1,28} = 0.93$, $P > 0.05$). In the young subjects, rMT was 36.9 ± 9.5% of stimulator output (SO) in the right hemisphere and 35.5 ± 7.0% SO in the left hemisphere. In the old subjects, rMT was 39.4 ± 7.8% SO in the right hemisphere and 38.2 ± 7.4% SO in the left hemisphere.

The measured rMT correlated highly with the prMT in both the left ($r = 0.82$, $P \leq 0.0001$) and right ($r = 0.92$, $P \leq 0.0001$) hemispheres. There was no effect of hemisphere ($F_{1,27} = 2.1$, $P > 0.05$) or age ($F_{1,27} = 0.26$, $P > 0.05$) on prMT. The interaction term was also not significant ($F_{1,27} = 2.3$, $P > 0.05$).

Stimulus-response characteristics. The group stimulus-response curves for young and old subjects are shown in Fig. 2. As expected, MEP amplitude increased with increasing stimulus intensity ($F_{1,22} = 104.3$, $P \leq 0.0001$) before reaching a plateau. There was no difference between the age groups in the range of stimulator intensities over which MEPs were evoked (i.e., the stimulus intensity at which MEP_{max} was evoked minus the stimulus intensity at which rMT occurred). There was no effect of hemisphere ($F_{1,12} = 2.3$, $P > 0.05$), indicating that the stimulus-response characteristics of the responses

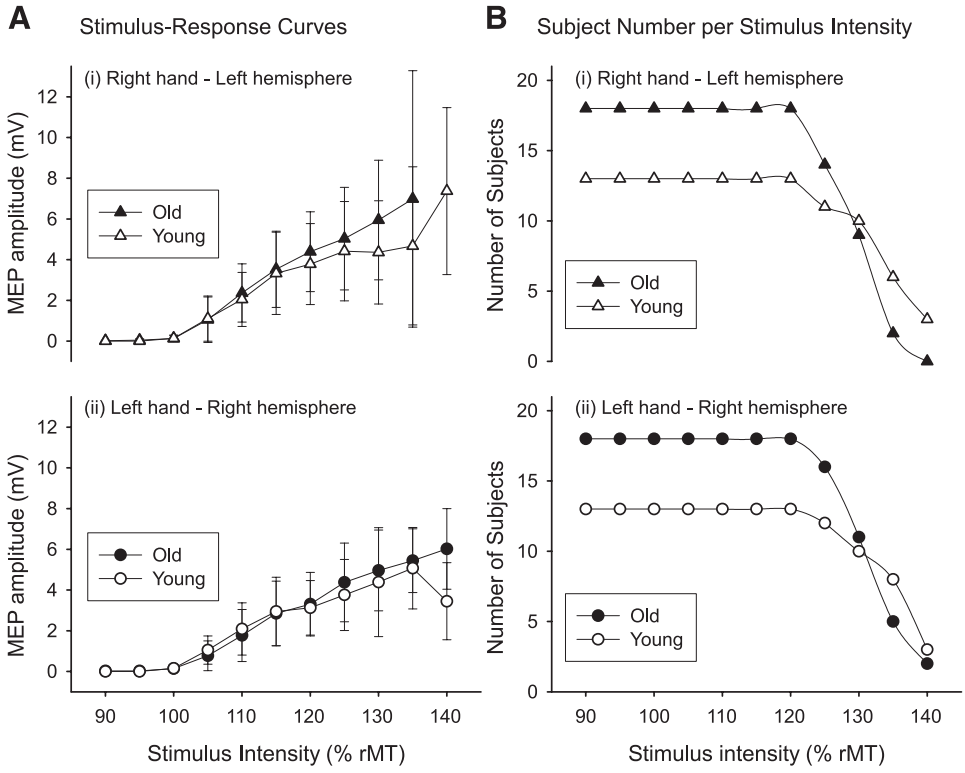

Fig. 2. *A*: stimulus-response curves for young and old subjects evoked from the right FDI (left M1; *i*) and left FDI (right M1; *ii*). FDI MEP amplitudes increased progressively from 100% rMT, and the rate of change and magnitude of MEP amplitude were similar in young and old subjects. Data are group mean ± SD MEP amplitude. *B*: no. of subjects for whom MEP data were obtained at each stimulus intensity to the group curves illustrated in *A*.

evoked in FDI were similar for both hemispheres. The increase in MEP amplitude with increasing stimulus intensity was not influenced by age ($F_{1,12} = 0.04$, $P > 0.05$), nor was there a hemisphere × age interaction ($F_{1,12} = 0.3$, $P > 0.05$).

Table 1 shows the curve characteristics derived from the fitted curves for young and old subjects. There was no difference in any of the characteristics when young and old men were compared or when hemispheres were compared.

Variability of muscle evoked potentials. Figure 3 shows the MEP CV at each stimulus intensity for young and old subjects. Overall, MEP CV was greater in the left hemisphere than the right ($F_{1,17} = 7.83$, $P = 0.01$), and there was a hemisphere × intensity × age interaction ($F_{8,17} = 2.27$, $P = 0.03$). Post hoc testing showed this was due to younger subjects having a greater MEP CV than old subjects at 125% rMT in the left hemisphere ($t = 2.68$, $P = 0.02$). Other than this, there was no difference in MEP CV due to age. When young and old subject data were pooled, there was an independent effect of hemisphere ($F_{1,18} = 7.25$, $P = 0.02$) and of intensity ($F_{8,144} = 29.68$, $P \leq 0.0001$) but no hemisphere × intensity interaction.

The strongest modulator of MEP CV was rMT, and covariate analyses showed an intensity × rMT interaction for the left hemisphere curve (contralateral rMT: $F_{8,152} = 4.50$, $P = 0.005$; ipsilateral rMT: $F_{8,152} = 5.45$, $P = 0.001$) and the right hemisphere curve (contralateral rMT: $F_{8,152} = 2.85$, $P = 0.03$; ipsilateral rMT: $F_{8,152} = 3.15$, $P = 0.02$). Subjects with low right hand FDI rMTs had a larger MEP CV at threshold in both the right hemisphere ($t = -2.34$, $P = 0.03$) and left hemisphere ($t = -3.08$, $P = 0.006$) stimulus-response curves. Similarly, subjects with a low left hand FDI rMT had larger MEP CV at threshold in the right hemisphere ($t = -2.47$, $P = 0.02$) and left hemisphere ($t = -3.65$, $P = 0.02$) curves.

M waves and F waves. Mean M-wave and F-wave data for the right FDI are shown for young and old men in Table 1. Younger men had larger M waves than older men ($F_{1,19} = 7.01$, $P = 0.02$). However, mean F-wave amplitude, chronodispersion, persistence, F-wave latencies, and the F-to-M ratio were not different when the age groups were compared. Figure 4 shows the right hand stimulus-response curves for the young and old subjects with MEP amplitude expressed as a ratio of the maximal M wave. Although there was a tendency for older men to have higher MEP-to-M wave ratios at higher stimulus intensities, this was not significant.

"Young" old compared with "old" old. The age range for the old group was 18 yr, i.e., from 55 to 73 yr. It is possible that the lack of age-related changes in the younger members of the old group masked the effects of aging evident in the older members of the group. To test this, the old group was divided into "young" old (aged 55–65 yr; $n = 10$) and "old" old (aged >65 yr; $n = 8$) and all analyses were repeated (i.e., the between-subjects factor age group had up to 3 levels: young, young-old, and old-old). In addition, regression analyses were performed for each of the different curve components with age in years as the dependent variable. There were no differences in corticospinal curves (all 3 age groups: $F_{2,28} = 0.97$, $P = 0.50$), any curve components [e.g., area under right hand curve ($F_{2,28} = 0.11$, $P = 0.89$); area under left hand curve ($F_{2,28} = 0.13$, $P = 0.88$)], or spinal (i.e., F wave) responses (mean amplitude: $F_{2,19} = 0.02$, $P = 0.98$; chronodispersion: $F_{2,19} = 1.53$, $P = 0.29$; persistence: $F_{2,19} = 0.13$, $P = 0.88$) when the

Table 1. *Curve characteristics for young and old subjects*

	Young	"Young" Old	"Old" Old	Old (All)
n	13	10	8	18
Age (range), yr	19.85 ± 1.63 (17–23)	60.4 ± 2.91 (55–64)	68.63 ± 2.45 (66–73)	64.06 ± 4.96 (55–73)
Laterality quotient	0.88 ± 0.11	0.95 ± 0.09	0.78 ± 0.29	0.90 ± 0.13
		Left FDI		
rMT (%SO)	36.85 ± 9.49 (28–61)	37.7 ± 6.19 (27–48)	41.13 ± 9.41 (25–54)	39.22 ± 7.60 (25–54)
prMT (% SO)	33.38 ± 9.29 (23.9–57.6)	35.75 ± 7.57 (22.76–41.7)	43.59 ± 14.51 (24.21–63.92)	39.17 ± 11.44 (22.8–64.0)
$Slope_{10\%}$	0.20 ± 0.44	0.17 ± 0.13	0.26 ± 0.33	0.22 ± 0.24
$Slope_{25\%}$	0.42 ± 0.93	0.29 ± 0.17	0.56 ± 0.74	0.42 ± 0.52
$Slope_{max}$	0.62 ± 1.22	0.38 ± 0.15	0.92 ± 1.15	0.63 ± 0.82
MEP_{max}, mV	4.66 ± 2.32	5.5 ± 2.34	5.09 ± 1.97	5.31 ± 2.13
AUC	0.92 ± 0.48	0.83 ± 0.34	0.85 ± 0.52	0.84 ± 0.42
		Right FDI		
rMT (% SO)	35.46 ± 7.01 (29–54)	37.6 ± 7.60 (28–52)	37.75 ± 7.92 (26–51)	37.67 ± 7.52 (26–52)
prMT (% SO)	33.44 ± 7.94 (23.6–50.6)	34.86 ± 6.2 (25.0–46.0)	34.53 ± 9.68 (20.8 ± 49.7)	34.70 ± 7.76 (20.1–49.7)
$Slope_{10\%}$	0.11 ± 0.08	0.11 ± 0.08	0.17 ± 0.16	0.14 ± 0.12
$Slope_{25\%}$	0.23 ± 0.16	0.25 ± 0.18	0.33 ± 0.27	0.29 ± 0.22
$Slope_{max}$	0.41 ± 2.32	0.45 ± 0.39	0.59 ± 0.61	0.51 ± 0.49
MEP_{max}, mV	4.73 ± 2.71	6.26 ± 3.21	5.30 ± 2.86	5.83 ± 3.01
AUC	0.97 ± 0.80	0.84 ± 0.38	0.92 ± 0.57	0.87 ± 0.46
M-wave amplitude, mV	20.29 ± 6.16	13.84 ± 3.42	16.41 ± 2.16	14.83 ± 3.18*
F-wave amplitude, mV	0.22 ± 0.07	0.21 ± 0.14	0.21 ± 0.08	0.21 ± 0.12
F-to-M ratio	0.011 ± 0.007	0.016 ± 0.11	0.011 ± 0.005	0.015 ± 0.009
Shortest F-wave latency, mV	27.3 ± 1.61	29.8 ± 2.82	29.7 ± 3.25	29.7 ± 2.77
F-wave chronodispersion, ms	3.24 ± 1.13	4.33 ± 1.45	4.45 ± 1.94	4.37 ± 1.56
F-wave persistence, %	95.6 ± 0.06	95.0 ± 0.06	94.0 ± 0.05	94.6 ± 0.05

Values are means ± SD for *n* subjects. FDI, first dorsal interosseous muscle; rMT, resting motor threshold; prMT, predicted rMT; SO, stimulator output; $slope_{10\%}$, $slope_{25\%}$, slope of curve at 10%, 25% of maximum stimulus intensity; $slope_{max}$, maximum slope; MEP_{max}, maximum motor evoked potential; AUC, area under the curve. *$P = 0.02$, young vs. old (all) subjects.

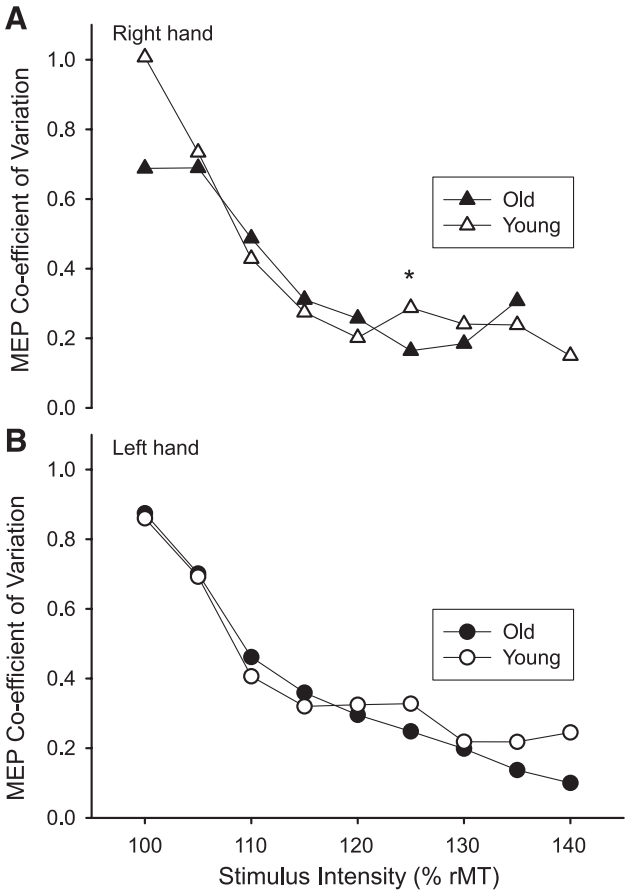

Fig. 3. Trial-to-trial variability [i.e., coefficient of variation (CV)] of right (*A*) and left (*B*) FDI MEP amplitude for young and old subjects at stimulus intensities ≥rMT. CV was highest at rMT and reduced quickly with increasing stimulus intensities to a plateau at ~20% above rMT. Overall, the CV was similar when young and old subjects were compared, although it was significantly higher for MEPs evoked in the right FDI of young subjects at a stimulus intensity of 20% above rMT compared with old subjects ($P = 0.02$).

two older age groups were compared or when the two older age groups were separately compared with the young group. In addition, age in years was not a significant factor in the magnitude of any of the curve components.

DISCUSSION

A number of previous studies have reported that there are changes in the excitability of the corticospinal stimulus-response curve associated with advancing age in humans (22, 23, 34). Only two studies have compared responses in men and women (23, 34), and the former suggested that any age-related changes may only be evident in women and not in men. The key finding in the present study is that when young men aged 17–23 yr are compared with older men aged 55–73 yr, there are no age-related changes evident in the corticospinal stimulus-response characteristics, either when the absolute MEPs are compared or when the MEP is corrected for maximal M-wave amplitude.

The finding that corticospinal responses are unchanged by aging in men are at odds with those of Talelli and colleagues (34). Unlike the present study, where stimulus-response curves were constructed with the muscle relaxed, Talelli et al. constructed FDI stimulus-response curves (in men and women) with a background contraction of 15–20% maximum voluntary contraction (MVC) and reported a negative correlation between age and the amplitude of the MEP at every stimulus intensity except threshold. No change was evident in either curve slope or M-wave amplitude, and no association with subject sex was found for any of the TMS parameters measured. One explanation for the discrepancies between the present study and the study of Talelli et al. (34) is that the aging process differentially affects the cortical circuits responsible for generation of I waves in the descending volley and this is only evident during voluntary contraction. It is generally accepted that different neural structures contribute to the generation of the early (i.e., I_1 and I_2) and later (i.e., I_3 and I_4) I waves produced by TMS since they are selectively activated by different coil orientations (2, 4, 11, 28). While we have no direct supporting evidence from this study, there is evidence from others that age-related changes in either the early or the later I waves may only be evident when there is voluntary contraction.

Epidural and EMG recordings from the FDI muscle during TMS show that, compared with rest, voluntary contraction significantly increases the magnitude and number of descending volleys and the EMG amplitude at the muscle (5). Spinal excitability is increased to a greater degree than cortical excitability as the threshold TMS intensity for evoking I waves is only marginally reduced by contraction (5). Therefore, less I-wave summation is required at the spinal motoneuron pool in order to produce an MEP when the muscle is contracted compared with when it is at rest. This raises the possibility that the relative contributions of the different early-phase I waves to the MEP may differ under the two conditions, particularly at different stimulus intensities. This is best explained with a hypothetical example: with voluntary contraction, only I_1 and I_2 waves may be needed to produce an MEP. However, at rest, I_1, I_2, and I_3 summation may be required to produce an MEP. If aging selectively affects only either I_1 or I_2 waves, this may

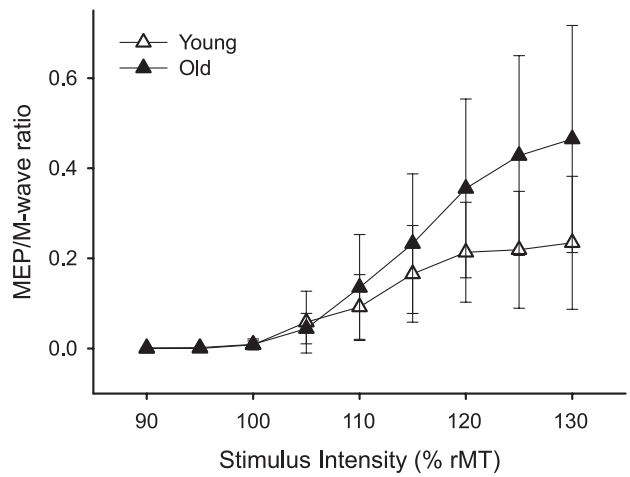

Fig. 4. Stimulus-response curves for young and old subjects when the MEP amplitude at each stimulus intensity is expressed relative to the maximal M wave. Data are group mean ± SD MEP-to-M wave ratios. Old men had significantly smaller M waves than young men, and this was reflected in the tendency to have greater MEP-to-M wave ratios. However, the difference was not statistically significant.

only be evident during voluntary contraction, when fewer I waves are contributing to the MEP.

An alternative explanation is that aging selectively affects the neural elements responsible for the later I waves, but this is not evident unless MEPs or the individual I-wave components of the descending volley are recorded with a sufficiently intense background contraction. Di Lazzaro and colleagues (5) recorded I_1, I_2, I_3, and I_4 waves in the descending volley both at rest and with a 20% MVC background contraction. With contraction I_4 waves were evident at stimulus intensities above ~120% of active motor threshold, whereas in resting muscle intensities above ~130% of active motor threshold were required. The amplitudes of the I_4 waves (but not the I_1–I_3 waves) evoked in the contracted muscle were significantly larger than those evoked by TMS at rest. I_4 waves are more likely to have contributed to MEP amplitudes in the study of Talelli et al. (34), where stimulus-response curves were constructed against a 20% MVC background contraction, and unlikely to have contributed to MEP amplitude in the present study, where the muscle was relaxed.

As Di Lazzaro and colleagues (5) point out, not all of the increased excitability associated with voluntary contraction will translate into facilitation, and at least some of this descending input may have an inhibitory effect at the spinal level. As well as reciprocal inhibition at the spinal level, it has recently been shown that voluntary contraction is also associated with cortical reciprocal inhibition (12). Reciprocal inhibition refers to the scaling of activation of the agonist muscle in a movement with the activation of its antagonist to optimize the movement. Hortobágyi et al. (12) showed that cortical and spinal reciprocal inhibition are both reduced in aging humans, leading to abnormally high coactivation between agonists and antagonists. Taken together, the findings from these studies regarding aging, TMS, and voluntary activation suggest that the influences on corticospinal stimulus-response characteristics when measured with a background muscle contraction are complex and not simply related to lowering the corticospinal activation threshold. Therefore, comparisons between the present study, where corticospinal curves were constructed in the resting, uncontracted muscle and the study of Talelli et al. (34), where curves were constructed against a background contraction of 20% MVC, are probably not valid.

As has been demonstrated numerous times before, MEP CV is greatest at stimulus intensities near rMT and declines with increasing stimulus intensities. Pitcher et al. (23) reported that the MEP CV was greater in women than in men and sex interacted with rMT and age to influence MEP CV. While the present study also showed that rMT strongly modulates MEP CV, rMT did not interact with age. Subjects with the highest rMTs had less MEP variability at a given stimulus intensity than subjects with low rMTs. There was no difference in the CV in MEP amplitudes when young and old men were compared, except at 25% stimulator output above rMT in the left hemisphere, where MEP CV was larger in young men (Fig. 3). While statistically significant, there is no obvious physiological explanation for this. Taken together with those of Pitcher et al. (23), these findings indicate that age and rMT only interact to influence MEP CV in women and not in men.

In addition to changes in cortical excitability, MEP amplitude is also sensitive to changes in excitability of the spinal motoneurons since suprathreshold TMS activates both neuron pools. Therefore it is possible that the site of any age-related change occurs at either or both segmental levels. Similarly, it is possible (though perhaps less likely) that a reduction in excitability at one level may be compensated for by an increase in excitability at the other. We assessed the excitability of the spinal motoneuron pool for FDI in the resting condition by evoking F waves, which have been shown to be sensitive to changes in motoneuronal excitability (8, 20). There were no detectable age-related differences in F-wave amplitude, latency, or chronodispersion or persistence or the F-to-M-wave amplitude ratio. While F-wave testing arguably only reflects excitability of the larger motoneurons (13), the lack of change in either this measure of spinal excitability or the MEP suggests that overall corticospinal excitability was preserved in this sample of aging men.

The amplitude of the M wave in a range of muscles declines with increasing age in humans (9, 29, 30). This is probably due to decline in motor unit numbers and distribution remodeling, which leads to fewer but larger motor units as well as an overall decline in muscle mass, i.e., sarcopenia (reviewed in Ref. 6). Shima and colleagues (30) reported a 26% reduction in tibialis anterior M-wave amplitude when 21- to 33-yr-old men were compared with 75- to 83-yr-old men but no reduction in central activation (determined by twitch interpolation). This is not dissimilar to the present findings of a 37% reduction in FDI M-wave amplitude when old men were compared with young men but no reduction in corticospinal excitability. Age-related loss of motor units has been reported to be greater in distal muscles such as FDI (9) and may partly explain the greater decline in M-wave amplitude found here.

Taken together with the findings of Pitcher et al. (23), the present results support the notion that there are sex differences in age-related changes in human motor cortical stimulus-response characteristics. In women of reproductive age, estrogen and progesterone not only regulate the menstrual cycle but also have profound effects on cortical excitability (32, 33). In aging women, the loss of these neuroactive hormones at menopause is likely to significantly alter motor cortex excitability. Unlike the sudden loss of estrogen with menopause in women, aging men do not generally undergo the same rapid changes in testosterone. To our knowledge, it is unknown whether age-related changes in testosterone alter motor cortex excitability in men, although Bonifazi et al. (1a) demonstrated that a single intramuscular injection of human chorionic gonadotropin that increased testosterone in young men 150% above preinjection levels also increased cortical excitability to TMS. But while sexually dimorphic age-related changes in the levels of neuroactive sex hormones such as estrogen, progesterone, and testosterone offer the most parsimonious explanation for our findings [when taken together with those of Pitcher et al. (1a)], we offer no direct evidence here to support this.

In conclusion, we found no age-related changes in motor cortical stimulus-response characteristics in male subjects when measured in the resting muscle. Since both previous studies that have reported age-related changes in motor cortical excitability included women and men, it is likely that this is due to changes inherent in the female participants. Further studies to assess the relationship between age-related changes in sex hormone levels and corticospinal excitability in men and women are warranted, since there is reason to hypothesize that the preservation of motor function in the elderly may be

facilitated by interventions (e.g., hormone replacement therapy) or lifestyle factors that maintain bioactive sex hormone levels. We are currently examining these issues in a new cohort of men and women.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

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