

Force control during submaximal isometric contractions is associated with walking performance in persons with multiple sclerosis

Original

Force control during submaximal isometric contractions is associated with walking performance in persons with multiple sclerosis / Davis, L. A.; Alenazy, M. S.; Almklass, A. M.; Feeney, D. F.; Vieira, T.; Botter, A.; Enoka, R. M.. - In: JOURNAL OF NEUROPHYSIOLOGY. - ISSN 0022-3077. - STAMPA. - 123:6(2020), pp. 2191-2200. [10.1152/jn.00085.2020]

Availability:

This version is available at: 11583/2838385 since: 2020-12-01T10:32:30Z

Publisher:

American Physiological Society

Published

DOI:10.1152/jn.00085.2020

Terms of use:

This article is made available under terms and conditions as specified in the corresponding bibliographic description in the repository

Publisher copyright

(Article begins on next page)

Submitted to: *Journal of Neurophysiology*

Resubmitted: March 23, 2020

Force control during submaximal isometric contractions is associated with walking performance in persons with multiple sclerosis

Leah A. Davis, Mohammed S. Alenazy, Awad M. Almuklass, Daniel F. Feeney, Taian Vieira,
Alberto Botter, Roger M. Enoka

Department of Integrative Physiology
University of Colorado Boulder, CO, USA

Leah Davis: leah.davis@colorado.edu (Corresponding Author)

Department of Integrative Physiology
University of Colorado Boulder
Campus Box 354
Boulder, CO 80309, USA
303-492-4975

Mohammed Alenazy: moal4255@colorado.edu

Department of Integrative Physiology
University of Colorado Boulder
Boulder, CO 80309, USA
College of Medicine
Majmaah University
Majmaah, Saudi Arabia

Awad Almuklass: awad.almuklass@colorado.com

College of Medicine
King Saud bin Abdulaziz University for Health Sciences
Riyadh, Saudi Arabia
King Abdullah International Medical Research Center (KAIMRC)
Riyadh, Saudi Arabia
Department of Integrative Physiology
University of Colorado
Boulder, CO, USA

36 Daniel Feeney: daniel.feeney@colorado.edu

37 Boa Technologies
38 Boulder, CO, USA

39 Taian Vieira: taian.vieira@polito.it

40 PolitoBIOMed Lab
41 Politecnico di Torino
42 Turin, Italy
43 Department of Electronics and Telecommunications
44 Politecnico di Torino
45 Turin, Italy

46 Alberto Botter: alberto.botter@polito.it

47 PolitoBIOMed Lab
48 Politecnico di Torino
49 Turin, Italy
50 Department of Electronics and Telecommunications
51 Politecnico di Torino
52 Turin, Italy

53 Roger Enoka: enoka@colorado.edu

54 Department of Integrative Physiology
55 University of Colorado Boulder
56 Boulder, CO 80309, USA
57

58

59

60

61 **Abstract**

62 Individuals with multiple sclerosis (MS) experience progressive declines in movement
63 capabilities, especially walking performance. The purpose of our study was to compare the
64 amount of variance in walking performance that could be explained by the functional capabilities
65 of lower leg muscles in persons with MS and a sex- and age-matched control group. Participants
66 performed two walking tests (6-min walk and 25-ft walk), strength tests for the plantar flexor and
67 dorsiflexor muscles, and steady submaximal (10% and 20% maximum) isometric contractions.
68 High-density electromyography (EMG) was recorded during the steady contractions and the
69 signals were decomposed to identify the discharge times of concurrently active motor units.
70 There were significant differences between the two groups in the force fluctuations during the
71 steady contractions (force steadiness), the strength of the plantar flexor and dorsiflexor muscles,
72 and the discharge characteristics during the steady contractions. Performance on the two
73 walking tests by the MS group was moderately associated with force steadiness of the plantar
74 flexor and dorsiflexor muscles; worse force steadiness was associated with poorer walking
75 performance. In contrast, the performance of the control group was associated with muscle
76 strength (25-ft test) and force steadiness of the dorsiflexors and variance in common input of
77 motor units to the plantar flexors (6-min test). These findings indicate that a reduction in the
78 ability to maintain a steady force during submaximal isometric contractions is moderately
79 associated with walking performance of persons with MS.

80 **New & Noteworthy.** *The variance in walking endurance and walking speed was associated with*
81 *force control of the lower leg muscles during submaximal isometric contractions in individuals*
82 *with MS. In contrast, the fast walking speed of a sex- and age-matched control group was*
83 *associated with the strength of lower leg muscles. These findings indicate that moderate*

84 *declines in the walking performance of persons with MS are more associated with impairments*
85 *in force control rather than decreases in muscle strength.*

86 **Keywords.** Multiple sclerosis, walking, force steadiness, common drive, motor units, high-
87 density EMG

88 **Introduction**

89 Multiple sclerosis (MS) is a demyelinating neurological disorder that compromises function
90 within the central and peripheral nervous systems. The damage caused by the disease invariably
91 leads to increases in self-reported levels of fatigue, worse walking and balance, and decreased
92 quality of life. When walking at a preferred speed, for example, individuals with MS take
93 shorter, wider, and more variable strides and spend a greater percentage of the gait cycle in the
94 double-support phase (Benedetti et al. 1999; Comber et al. 2017; Galea et al. 2017; Gutierrez et
95 al. 2005; Sosnoff et al. 2012). These declines in gait kinematics are associated with a greater
96 energetic cost of walking for persons with MS (Motl et al. 2012; Sebastião et al., 2018), which
97 may contribute to the elevated levels of fatigue they report (Hadjimichael et al. 2008; Kluger et
98 al. 2012; Loy et al. 2017; Zijdwind et al. 2016).

99 The mobility-limiting symptoms experienced by persons with MS arise in part from the
100 progressive decline in sensorimotor function (Cabib et al. 2015; Newsome et al. 2011;
101 Zackowski et al. 2015). The disease compromises functional connectivity within the central
102 nervous system (Fling et al. 2015, Fritzer et al. 2017; Schlaeger et al. 2015), including the
103 activation signal sent from the spinal cord to muscle (DeLuca et al. 2013; Kearney et al. 2015;
104 Petrova et al. 2018). These changes result in a decrease in the maximal capacity to activate
105 muscle (Andreasen et al. 2009; Ng et al. 2004), a reduction in the number of functioning motor
106 units (Vogt et al. 2009), and a lesser range of rate coding for single motor units (Rice et al.
107 1992). Consistent with these observations, we have found that the normalized amplitude of the
108 force fluctuations and the mean interspike interval of motor unit action potentials in plantar
109 flexor muscles during steady submaximal contractions can explain moderate, but significant,

110 amounts of the variance in performance of individuals with MS on tests of maximal walking
111 speed and walking endurance (Almuklass et al. 2018).

112 Technological advances in electromyography (EMG) now make it possible to evaluate more
113 thoroughly the influence of the impairments in muscle activation on the capacity of an individual
114 to control muscle force (Farina et al. 2016). In particular, multi-channel electrode systems
115 enable the decoding of the neural drive to muscle by identifying the discharge times of several
116 concurrently active motor units from surface EMG recordings (Farina et al. 2010). In a seminal
117 study, for example, Negro et al. (2009) demonstrated that the first principal component of the
118 smoothed discharge rates of ≥ 4 motor units in a hand muscle was strongly correlated ($72 \pm 13\%$)
119 with the fluctuations in abductor force applied by the little finger during steady submaximal
120 contractions. They found a similar association ($58 \pm 14\%$) for motor units in tibialis anterior
121 when the dorsiflexors performed a steady, isometric contraction at 10% maximal voluntary
122 contraction (MVC) force. Subsequently, Thompson et al. (2018) demonstrated with an *in vivo*
123 cat model that the cumulative spike trains of ≥ 9 motor units were strongly correlated with both
124 the total force ($99.2 \pm 0.2\%$) and the higher frequency force fluctuations ($83.5 \pm 1.3\%$) evoked in
125 the soleus muscle.

126 The normalized amplitude of the force fluctuations (coefficient of variation for force) during
127 steady submaximal contractions provides a measure of force steadiness (Galganski et al. 1993).
128 Force steadiness is a sensitive marker of fine motor control as it varies with the target force for
129 the steady contraction (Galganski et al. 1993; Laidlaw et al. 2000; Tracy and Enoka, 2002), the
130 test muscle (Grunte et al. 2010; Tracy et al. 2007), the difficulty of the task (Almuklass et al.
131 2016; Holmes et al. 2015), the level of physiological arousal (Christou et al. 2004; Pereira et al.
132 2015; Rice et al. 2015), the age of the performer (Castronovo et al. 2018; Hamilton et al. 2017;

133 Marmon et al. 2011), and the neurological health of the individual (Bilodeau et al. 2000; Carville
134 et al. 2007; Gould et al. 2018). Critically, force steadiness has consistently emerges as a
135 statistically significant explanatory variable for the variance in performance on a number of
136 dynamic tasks, such as walking (Almuklass et al. 2018, Mani et al. 2018), manual dexterity
137 (Almuklass et al. 2016, Feeney et al. 2018; Hamilton et al. 2017; Marmon et al. 2011), risk of
138 falls in older adults (Carville et al. 2007), and postural sway (Davis et al. 2020).

139 The purpose of our study was to compare the amount of variance in walking performance that
140 could be explained by the functional capabilities of lower leg muscles in persons with MS and an
141 age- and sex-matched control group. Walking performance was quantified as fast walking speed
142 (25-ft test) and walking endurance (6-min test), whereas muscle function was characterized with
143 measures of muscle strength, force steadiness during submaximal isometric contractions, and the
144 discharge characteristics of single motor units during the steady contractions. Due to the
145 explanatory power of force steadiness for the performance of older adults on tests of motor
146 function, we hypothesized that significant amounts of the variance in walking performance for
147 individuals with MS would be explained by differences in force steadiness, whereas we expected
148 measurements of muscle strength to be the dominant explanatory variable for the control group.

149 **METHODS**

150 *Subjects*

151 Data from 18 participants with relapsing-remitting MS who participated in a previous study (52
152 ± 8 yrs, 7 men, 3.6 ± 0.96 PDDS; Almuklass et al., 2017, Almuklass et al., 2018) were compared
153 with 18 sex- and age-matched (± 5 yrs) control subjects (52 ± 9 yrs) who reported no
154 neurological diseases. The control subjects were explicitly recruited for our current report. The
155 MS participants provided written informed consent (IRB#: 13-0720) for the previous study. For

156 the current study, a waiver-of-consent document was approved in accordance with the exception
157 to the regulations of the Office of Human Research Protections in that there was no more than
158 minimal risk of harm to subjects and it involved no procedures for which written consent is
159 normally required outside the research context. The MS subjects were sent an approved e-mail
160 message that requested permission to use their data by replying either ‘yes, I consent for you to
161 use my data’ or ‘no, I do not consent for you to use my data.’ The control group provided
162 written informed consent to participate in a protocol (IRB#: 16-0396) that was approved by the
163 Institutional Review Board at the University of Colorado.

164 The MS participants completed a baseline evaluation over a 2-day period that included
165 measurements of muscle strength, force steadiness, walking endurance, and fast walking speed
166 (Almuklass et al., 2017). They then performed a 6-wk intervention in which neuromuscular
167 electrical stimulation was applied to their plantar flexor and dorsiflexor muscles 3x/wk for a total
168 of 18 treatment sessions. The current report includes only those data that were obtained from the
169 MS participants during the baseline evaluation. These baseline data were compared with those
170 for the control group that was collected using the same protocol performed by the MS group, but
171 within a single session.

172 ***Strength and force steadiness.***

173 Both groups performed measurements of muscle strength and force steadiness with the
174 dorsiflexor and plantar flexor muscles. Participants lay in a supine position with the hip and
175 knee joints at neutral angles and the ankle at 90°. A strap was placed around the widest section
176 of the forefoot and connected to a strain-gauge transducer (MLP-300, Transducer Techniques,
177 Temecula, CA). The force signal was sampled at 1 kHz (Power 1401, Cambridge Electronic
178 Design, Cambridge, UK) and displayed on a monitor that was placed ~1 m in front of the

179 participants. They performed maximal voluntary contractions (MVC) with the ankle-spanning
180 dorsiflexor and plantar flexor muscles; the task was to increase muscle force gradually (~30%
181 MVC/s) up to maximum and then sustain it for ~ 3 s. They were verbally encouraged to provide
182 a maximal effort during each MVC. They performed 2-5 MVCs until the peak forces in 2 trials
183 were within 10% of each other, the greater of which was taken as the MVC force. The moment
184 arm for the muscle torque calculation was measured as the distance from the lateral malleolus to
185 the center of the strap around the forefoot.

186 Participants then performed submaximal isometric contractions for ~30 s while matching target
187 forces of 10% or 20% MVC force (Figure 1. A and B). The submaximal contractions were
188 performed with the dominant leg (Waterloo footedness questionnaire) by the control group and
189 in the self-reported leg with fewer symptoms (less-affected leg) by the MS group. The task was
190 to increase the force from an initial resting value up to the target force displayed on a monitor
191 (visual angle $\sim 0.25^\circ$) and then to maintain a steady contraction for ~30 s. Participants were not
192 asked to achieve a specific a rate of increase in force, but typically reached the target force ≥ 2 s
193 ($\sim 5 - 10\%$ MVC/s). Participants performed two trials at each target force for both muscle
194 groups.

195 The force signals were amplified (Coulbourn Instruments, Allentown, PA) and then recorded on
196 a computer with Spike2 data acquisition software (Version 6.17, Cambridge Electronic Design,
197 Cambridge, UK). The force signals were subsequently low-pass filtered with a cut-off frequency
198 of 20 Hz and the fluctuations in force during the steady contractions (force steadiness) were
199 quantified as the coefficient of variation for force (Galganski et al., 1993).

200 ***High-density surface EMG.***

201 Three high-density surface electrodes (4x8 detection points, 10 mm interelectrode distance) were
202 placed longitudinally over the tibialis anterior, medial gastrocnemius, and lateral portion of the
203 soleus muscles during the steady isometric contractions (Figure 1.A; plantar flexors or
204 dorsiflexors x two target forces x two trials at each target force). A custom MATLAB script was
205 used to decompose motor unit activity from the EMG signals (Figure 1, C and D; Holobar &
206 Zazula, 2007).

207 [Figure 1]

208 The interspike intervals (ISI) for each motor unit were calculated as the difference between
209 consecutive discharge times. Due to limitations in decomposition algorithms, the signals likely
210 contained both motor unit signals as well as non-physiological waveforms. To control for
211 aberrant waveforms, the decomposed signal was deemed not to be a motor unit when all four of
212 the following criteria were met: 1) $25 < \text{ISI} < 400$ ms; 2) $8\% < \text{coefficient of variation for ISI} <$
213 55% ; 3) if the skewness of the ISI histogram was between -0.5 and 0.5; and 4) if the coefficient
214 of variation for ISI was $<10\%$ *and* the skewness of the ISI histogram was <1 (Almuklass et al.,
215 2018).

216 When the discharge times of ≥ 5 motor units were identified for a given trial, the data were
217 entered into a state-space model (Feeney et al., 2017, Macke et al., 2011) to estimate the variance
218 in the common synaptic input to the motor neuron pools during the steady contractions. Briefly,
219 the unobserved common input at a given time, $x(t)$, is related to a linear approximation of the
220 common input (A) at the previous time point, the influence of the intended target force on
221 discharge rate ($bf(t)$), and the effects of synaptic noise on signal transmission as represented as a
222 Gaussian noise vector ($E(t)$). The target force is represented by $f(t)$, which is influenced by a
223 vector representing discharge rate saturation in low threshold motor units (b)

$$\mathbf{x}(t) = \mathbf{A}\mathbf{x}(t - 1) + \mathbf{b}f(t) + \mathbf{E}(t)$$

224 The common synaptic input varies over the contraction and is modeled with Poisson linear
225 dynamics.

$$x_i \sim N(x_o, Q_o)$$

$$x_t | x_{t-1} \sim N(Ax_{t-1}, bf_t, Q)$$

226 The term Q represents the variance in the state-space trajectory, which corresponds to the
227 fluctuations in the common input signal. Q is assumed to remain constant during each steady
228 contraction.

229 Motor unit discharge times were sorted into 10-ms bins and arranged into a binary matrix where
230 the occurrence of an action potential was represented by 1. The matrix was entered into an open
231 source Expectation-Maximization algorithm (Macke et al., 2011; Buesing et al., 2012) to
232 estimate the parameters of the state-space model. The Q values were subsequently low-pass
233 filtered to account for the response characteristics of muscle. The unfiltered Q values were
234 interpreted as the variance in the common synaptic input received by the motor neuron pool,
235 whereas the filtered Q values estimated the variance in the activation signal received by the
236 muscles.

237 ***Walking tests.***

238 Each participant performed two walking tests: 25-ft walk (fast walking speed) and the 6-min
239 walk (walking endurance). Fast walking speed was represented as the average of two 25-ft tests.
240 Participants stood ~1 m before the start line and a timer was started as soon as one foot stepped
241 over the line and stopped when one foot stepped over the end line. The 6-min test required
242 participants to walk around an indoor track for 6 minutes and the distance covered was

243 measured. The instruction for both tests was to walk as quickly but as safely as possible. Due to
244 the influence of fatigue on the performance of persons with MS, they performed the two walking
245 tests on one day and the tests of muscle function on another day. The control subjects performed
246 all the tests on the same day.

247 *Questionnaires.*

248 The disability status of the MS participants was quantified with three questionnaires: patient
249 determined disease steps (PDDS), MS walking scale-12 (MSWS-12), and modified fatigue
250 impact score (MFIS). Only the PDDS scores are reported here.

251 *Data Analysis.*

252 Descriptive statistics for both pairwise and group values were calculated and are reported as
253 mean \pm standard deviation. Pairwise differences across groups were calculated as the absolute
254 difference between paired subjects for each variable. When the 95% confidence interval of the
255 differences included 0, the difference was deemed not to be statistically significant. Conversely,
256 the absence of 0 in the 95% confidence interval corresponded to a statistically significant
257 pairwise difference. Group differences were examined with linear regression analysis for each
258 variable ($P < 0.05$). Muscle strength was compared between 1) the less-affected leg from the MS
259 group to the dominant leg from the control group, and 2) the more-affected leg of the MS group
260 and the non-dominant leg of the control group. Due to the variable numbers of motor units
261 across subjects, we could only examine group differences for both the filtered and unfiltered Q
262 values.

263 Pearson-product correlations were used to compare performance on the walking tests (25-ft test
264 and 6-min test) with muscle strength, force steadiness, and the variability in common input (Q)
265 for each group of participants. Significantly correlated variables were entered in a backward

266 linear regression analysis to identify the measures of muscle function that were most strongly
267 associated with the variability in walking performance for each group.

268 All statistical procedures were performed in R (Version 3.5.1) with an α level of $P < 0.05$ (with
269 Bonferroni correction for multiple comparisons) for statistical significance.

270 **RESULTS**

271 The results comprise an assessment of the associations between walking performance and
272 measures of muscle function and motor unit activity in lower leg muscles of persons with MS
273 and an age- and sex-matched control group.

274 *Strength, force steadiness, and walking.*

275 Table 1 contains the pairwise and group differences for the measurements of force steadiness and
276 muscle strength. In contrast to the control group, force steadiness (coefficient of variation for
277 force) for both the plantar flexors and dorsiflexors was not less at the greater target force (20%
278 MVC) than the lower target force (10% MVC) for the MS group. However, force steadiness for
279 the dorsiflexors of both groups was greater at the two target forces than that for the plantar
280 flexors. Nonetheless, there were no significant differences between groups in force steadiness of
281 the plantar flexors at either target force (10% or 20% MVC) and in the force steadiness for the
282 dorsiflexors at 10% MVC. At the greater target force (20% MVC) for the dorsiflexors, however,
283 the MS participants exhibited significantly worse force steadiness (greater force fluctuations)
284 than the control group.

285 [Table 1]

286 There were no statistically significant differences in MVC torque between legs for the plantar
287 flexor muscles of each group of participants and for the dorsiflexor muscles in the control group.

288 In contrast, dorsiflexor MVC torque for the more-affected leg was significantly less for the less-
289 affected leg in the MS group. Further, the MS group was consistently weaker than the control
290 group for both the plantar flexor and dorsiflexor muscles of each leg.

291 The difference in time to complete the 25-ft walk test between the MS and control groups was
292 not statistically significant despite substantially different group means. This was due to the large
293 standard deviation for the MS group (Table 2). In contrast, the control group walked further
294 during the 6-min walk test at each recorded timepoint (1 min, 2 min, 4 min, and 6 min) than the
295 MS group. Furthermore, the absolute difference in distance walked between participants
296 matched across groups increased progressively during the 6-min test (Table 2).

297 [Table 2]

298 ***Motor units.***

299 Motor unit data were recorded for the tibialis anterior, medial gastrocnemius, and soleus muscles
300 during the submaximal contractions at the two target forces. Our analysis required ≥ 5 identified
301 motor units in each trial in order to calculate Q (Feeney et al., 2017). As the 19 participants in
302 each group performed 2 trials for every condition, there was the possibility of recording usable
303 data from 38 trials for each muscle group at each target force. However, the number of viable
304 trials was less than 38 for both the MS and control groups, respectively: tibialis anterior (10%
305 MVC: 24 and 32 trials; 20% MVC: 30 and 36 trials), soleus (10% MVC: 13 and 20 trials; 20%
306 MVC: 18 and 25 trials), and medial gastrocnemius (10% MVC: 6 and 20 trials; 20% MVC: 14
307 and 21 trials). Thus, it was more difficult to identify a sufficient number of motor units in the
308 MS participants than the control group and in the plantar flexor muscles than the dorsiflexor
309 muscle. Due to the shared contribution of medial gastrocnemius and soleus to the net plantar

310 flexor torque, the discharge times of motor units recorded from the medial gastrocnemius and
311 soleus were pooled and the variance in the common input (Q) was calculated for the pooled data.

312 When performing a steady isometric contraction at 10% MVC force with the dorsiflexor
313 muscles, the mean and coefficient of variation for interspike interval for motor units in tibialis
314 anterior were greater and the unfiltered Q value was lower for the MS group than the control
315 group (Table 3). At the higher target force (20% MVC), only the coefficient of variation for
316 interspike interval of motor units in tibialis anterior was greater for the MS group than the
317 control group (Table 3).

318 There were fewer group differences in motor unit activity during the steady contractions
319 performed with the plantar flexor muscles. The most consistent difference between the groups
320 was the lower unfiltered Q values (medial gastrocnemius + soleus) for the MS group compared
321 with the control group at both target forces (10% & 20% MVC; Table 5). Also, the mean
322 interspike interval for motor units in medial gastrocnemius was greater at the 20% target force
323 for the MS group than the control group. Notably, there was only one statistically significant
324 difference for either group of participants in the mean and coefficient of variation for interspike
325 intervals across target forces (Table 4). Mean interspike interval for motor units in the tibialis
326 anterior of the control group were significantly lower at 20% MVC than at 10% MVC.

327 [Table 3, 4, & 5]

328 The filtered Q values for tibialis anterior were correlated with force steadiness in the dorsiflexor
329 muscles of the MS group. When the target forces (10 and 20% MVC) were pooled, the
330 correlation coefficient was 0.32 ($P = 0.04$) for the MS group and 0.23 ($P = 0.06$) for the control
331 group. The association between the filtered Q values from the tibialis anterior and force
332 steadiness of the dorsiflexors when the MS group maintained a steady contraction at 10% MVC

333 was not statistically significant when the data were not collapsed across target forces ($r = 0.37$, P
334 $= 0.10$). The filtered Q values from tibialis anterior and force steadiness for the dorsiflexors at
335 20% MVC were significantly correlated ($r = 0.45$, $P = 0.008$) in the control group. There were
336 no significant correlations between the filtered Q values and force steadiness of the plantar
337 flexors.

338 *Walking correlations and regression analyses.*

339 To assess the relative explanatory power of the outcome variables on the two tests of walking
340 performance, we first identified the variables that showed statistically significant correlations
341 with each walking test and then compared the relative influence of these correlations by
342 developing regression models that retained the most influential variables. Table 6 shows that
343 there were a greater number of significant Pearson-product correlations between muscle function
344 (force steadiness, strength, and motor unit discharge characteristics) and walking performance
345 for the MS group than for the control group. The distance walked in 6 min by the MS group was
346 correlated with three of the four measures of force steadiness, with the filtered Q values for the
347 motor units in the plantar flexors, and with the strength of the dorsiflexors in the more-affected
348 leg. The distance walked in 6 min by the control group was correlated with force steadiness for
349 the dorsiflexors at the lower target force and the filtered Q value for the plantar flexors.

350 The time it took the MS group to walk 25 ft was correlated with the same set of outcome
351 variables as for the 6-min walk, except not with the strength of the dorsiflexors in the more
352 affected leg. The time it took the control group to walk 25 ft was correlated with one measure of
353 force steadiness (plantar flexors at 10% MVC) and the strength of plantar flexors and
354 dorsiflexors of the left and right legs.

355 Four regression models were developed (2 groups x 2 tests of walking performance); each model
356 involved up to three variables with the strongest correlations to walking performance. The
357 regression model for the 6-min distance of the MS group explained 54% of the variance with two
358 predictor variables (Figure 2A): force steadiness of the plantar flexors at 20% MVC force (partial
359 $r = -0.52$) and force steadiness for the dorsiflexors at 10% MVC (partial $r = -0.36$). The
360 regression model for the 6-min distance of the control group explained 36% of the variance with
361 two predictor variables (Figure 2B): force steadiness of the dorsiflexors at 20% MVC force;
362 partial $r = -0.54$) and the filtered Q values for the plantar flexors (partial $r = -0.19$).

363 The regression model for the time it took the MS group to walk 25 ft explained 34% of the
364 variance with two predictor variables (Figure 2C): force steadiness of the plantar flexors at 20%
365 MVC force (partial $r = -0.47$) and force steadiness for the dorsiflexors at 10% MVC (partial $r =$
366 0.48). The regression model for the time it took the control group to walk 25 ft explained 56%
367 of the variance with two predictor variables (Figure 2D): MVC torque for the plantar flexors of
368 the non-dominant leg (partial $r = -0.49$) and MVC torque for the dorsiflexors of the dominant leg
369 (partial $r = -0.39$).

370 [Table 6 & Figure 2]

371 **DISCUSSION**

372 The main finding of our study was that moderate amounts of the variance in two tests of walking
373 performance for persons with MS and control participants were explained by measurements
374 derived from submaximal, isometric contractions with the plantar flexor and dorsiflexor muscles.
375 The exception to this general conclusion was that the explanatory variables for the fast walking
376 speed (25-ft test) performed by the control group were two measurements of muscle strength.
377 We hypothesized that significant amounts of the variance in walking performance would be

378 explained by differences in force steadiness for individuals with MS, whereas we expected
379 muscle strength to be the dominant explanatory variable for the control group.

380 ***Walking, strength, and force steadiness.***

381 We found that greater coefficients of variation in force (worse force steadiness) corresponded to
382 a shorter distance walked in 6 min in both groups of participants and to a longer time to walk 25
383 ft in the MS participants. These associations were stronger for the MS group than the control
384 group. The functional significance of force steadiness is that it represents an individual's
385 accuracy in producing and maintaining a force trajectory (Christou et al. 2003). Within the last 5
386 years, our lab has found that force steadiness, a measurement derived from submaximal
387 isometric contractions, consistently emerges as a significant explanatory variable in regression
388 models to explain the variance in performance of a dynamic task (Almuklass et al. 2016,
389 Almuklass et al. 2018, Davis et al. 2020, Feeney et al. 2018, Mani et al. 2018).

390 Although the direction of the correlations (positive or negative) has differed across studies, the
391 correlation coefficients and partial-r values have consistently comprised moderate-to-strong
392 values. Of particular note, when both force-steadiness values and muscle strength (MVC
393 torques) have both been entered into the regression models, force steadiness frequently has the
394 greater explanatory power for the variance in the outcome variables (Almuklass et al. 2016;
395 Hamilton et al. 2017; Justice et al. 2014; Mani et al. 2018; Marmon et al. 2011). Taken together
396 with previous research, these results suggest that an individual's ability to sustain a constant
397 force during a steady isometric contraction at a submaximal target force is more often
398 functionally relevant than maximum muscle strength for most activities of daily living. The
399 stronger correlations between walking performance and force steadiness for the MS group than
400 the control group suggests that the negative impact of the disease on the ability to sustain steady

401 submaximal contractions has functional consequences. Moreover, the underlying mechanisms
402 presumably involve the variance in the common input received by the activated motor neurons
403 (Feeney et al. 2017; Negro et al. 2009; Thompson et al. 2018).

404 The only case in which muscle strength emerged as a significant explanatory variable was for the
405 25-ft test performed by the control group. Stronger lower leg muscles were associated with
406 faster times to walk 25-ft (faster). As the goal of this test is to walk as quickly as possible for a
407 relatively short distance, the same relative muscle strength produces greater absolute forces and
408 faster gait cycles (Bohanan, 1997; Broekmans et al. 2012; Clark et al. 2013). Although muscle
409 strength did not emerge as an explanatory variable for the MS participants, dorsiflexor MVC
410 torque for the more-affected leg was negatively correlated with their walking endurance.

411 *Motor units.*

412 Previously, Almuklass et al. (2018) found that the walking performance of individuals with MS
413 ($n = 27$) was associated with the mean interspike intervals of single motor units in medial
414 gastrocnemius and soleus muscles during steady contractions (10% MVC force) averaged across
415 2 to 3 time points. The current study comprised the data obtained from a subset of these
416 participants ($n = 18$) in only one of the experimental sessions. In this reduced data set, we did
417 not find any significant associations between either the mean or the coefficient of variation for
418 interspike interval with performance on the two walking tests.

419 Instead of estimating the cumulative influence of motor unit activity by collapsing data across
420 experimental sessions (Almuklass et al. 2018), we derived Q values from the discharge times of
421 many motor units during steady submaximal contractions to infer the activity of the motor unit
422 pool. We found that lower filtered Q values for the plantar flexors of individuals with MS

423 corresponded to a longer time to complete the 25-ft test and a shorter distance walked in 6 min.
424 In contrast, the filtered Q value for the plantar flexors of the control group was negatively
425 associated with walking endurance, but not with fast-walking speed. These findings suggest that
426 greater variance in the common input to motor neurons, once it had been low-pass filtered by the
427 muscle, was associated with better walking endurance and faster walking speed in individuals
428 with MS, but with worse walking endurance in healthy adults. Although we hypothesized that
429 variance in the common input would be associated with better walking performance, we
430 expected the association to be for the dorsiflexors and not the plantar flexors.

431 The current study appears to be the first to examine the common input to the motor unit pool in
432 individuals with MS. The moderate correlations between the variance in the common
433 modulation of motor units within the tibialis anterior and force steadiness of the dorsiflexors are
434 consistent with previous work reported from our lab on the wrist extensor muscles (Feeney et al.
435 2018). In that study, they found that the unfiltered Q values derived from the discharge times of
436 motor units during a steady contraction at 20% MVC force were significantly correlated with
437 force steadiness for both young ($r^2 = 0.31$) and older ($r^2 = 0.39$) adults. However, only the
438 correlation for the older adults had a functional influence on the time it took older adults to
439 complete a pegboard test of manual dexterity. Perhaps these findings suggest that the functional
440 significance of the variance in common input is most evident in individuals with a reduced
441 integrity of the sensorimotor system.

442 A key issue that needs to be addressed in this field is the discrepancy in the magnitude of the
443 correlation between the variance in common input and force steadiness (fluctuations in force) for
444 the classic studies (Negro et al. 2009; Thompson et al. 2018) and our work (Feeney et al. 2018;
445 current study). One likely confounding factor is the number of muscles that contribute to the

446 applied force. Negro et al. (2009) studied the sole contributor to the abduction force exerted by
447 the little finger (abductor digiti minimi), whereas Thompson et al. (2018) examined the isolated
448 soleus muscle in a decerebrate cat preparation. In these two studies, 72% and 84%, respectively,
449 of the force fluctuations during steady contractions were explained by the estimated variance on
450 the common input signal of the activated motor units. In contrast, the current study assessed the
451 association between the net force and motor units in just a few of the involved muscles. For
452 example, there are nine muscles that can contribute to the net plantar flexor force with each
453 muscle varying in architecture and lines of action. Although some evidence suggests that the
454 motor neuron pools of synergist muscles share most of their synaptic input (Laine et al. 2015),
455 the generalizability of this conclusion needs to be examined in a broader array of synergistic
456 muscles. Even among the dorsiflexor muscles where tibialis anterior contributes approximately
457 60% to the applied force (Andreassen & Arendt-Nielsen, 1987), the Q value calculated from the
458 discharge times of those motor units was only moderately associated with the force fluctuations
459 (current study and Negro et al., 2009). Moreover, it is the fluctuations in the net force rather than
460 the activity of a few selected motor units that is more strongly associated with motor
461 performance.

462 The variance in the common input in the current study was quantified using a state-space model,
463 which Feeney et al. (2017) used to model the variance of the common input signal to motor
464 neurons. This parameter differs from the cumulative spike train (CST) estimate, which explains
465 a large part of the fluctuations in the motor output from the spinal cord during isometric
466 contractions (Negro et al., 2009). To enable a more direct comparison with the estimate of the
467 variance derived from the CST, the Q values were filtered to mimic the low-pass filtering
468 influence of muscle on the variance in the common synaptic input to motor neurons (Farina et

469 al., 2014). Consistent with the classic finding of a significant association between CST values
470 and force fluctuations (Negro et al., 2009; Thompson et al., 2018), we found that it was the
471 filtered Q values that were significantly correlated for three of the four walking-test results
472 (Table 6). Moreover, the filtered Q values for the plantar flexors emerged as one of the two
473 significant explanatory variables for the distance walked in 6 min by the control group.
474 Although the unfiltered Q values for the motor units in the plantar flexors during the two steady
475 contractions (10% and 20% MVC) were greater for the control group, this difference did not
476 explain the variance in performance on the walking tests for either group of participants. Taken
477 together, these findings reveal some of the differences between the CST and state-space model
478 measures of variance in common input. It appears that the state-space model may approximate
479 the common input to the motor neurons, whereas the CST more accurately represents the
480 common output of the motor pool.

481 **Conclusion**

482 The time it took individuals with MS to walk 25 ft and the distance they could walk in 6 min
483 were most strongly associated with the fluctuations in force during steady, submaximal
484 contractions (force steadiness) with the plantar flexors and the dorsiflexors. In contrast, the 25-ft
485 time for the control group was associated with the strength (MVC torque) of the plantar flexors,
486 whereas their 6-min distance was explained by force steadiness for the dorsiflexors and the
487 variance in common input to the plantar flexors during the steady contractions. These findings
488 indicate that the ability to maintain a constant force during a submaximal, isometric contraction
489 has a greater influence than the strength of lower leg muscles on the walking performance of
490 persons with MS.

491

492 **Grants**

493 The Eunice Kennedy Shriver National Institute of Child Health and Human Development
494 provided support for the preliminary study in the MS group (R03 HD-079508). The current
495 study was not funded.

496

497 **Disclosures**

498 The authors have no conflicts of interest, financial or otherwise, to report.

499

500 **Author contributions**

501 L.A.D., A.M.A. and R.M.E. conceived and designed research; L.A.D., A.M.A., and M.S.A.
502 performed experiments; L.A.D, A.M.A, M.S.A, D.F.F, T.V., A.B., R.M.E interpreted results of
503 experiments; L.A.D, M.S.A, and R.M.E. prepared figures; L.A.D. and R.M.E. drafted
504 manuscript; L.A.D, A.M.A, M.S.A, D.F.F, T.V., A.B., R.M.E edited and revised manuscript;
505 L.A.D, A.M.A, M.S.A, D.F.F, T.V., A.B., R.M.E approved final version of manuscript.

506

507

508

509

510 **References**

- 511 Almuklass AM, Davis LA, Hamilton LD, Vieira TM, Botter A, Enoka RM. Motor unit discharge
512 characteristics and walking performance of individuals with multiple sclerosis. *J Neurophysiol*
513 119: 1273-1282, 2018.
- 514 Almuklass AM, Davis LA, Hamilton LD, Hebert JR, Alvarez E, Enoka RM. Pulse width does
515 not influence the gains achieved with neuromuscular electrical stimulation in people with
516 multiple sclerosis: double-blind, randomized trial. *Neurorehabil Neural Repair* 32: 84-93, 2018.
- 517 Almuklass AM, Price RC, Gould JR, Enoka RM. Force steadiness as a predictor of time to
518 complete a pegboard test of dexterity in young men and women. *J Appl Physiol* 120: 1410 –
519 1417, 2016.
- 520 Andreassen AK, Jakobsen J, Petersen T, Andersen H. Fatigued patients with multiple sclerosis
521 have impaired central muscle activation. *Mult Scler* 15: 818-827, 2009.
- 522 Andreassen B, Arendt-Nielsen L. Muscle fibre conduction velocity in motor units of the human
523 anterior tibial muscle: a new size principle parameter. *J Physiol* 391: 561-571, 1987.
- 524 Baert I, Freeman J, Smedal T, Dalgas U, Romberg A, Kalron A, Conyers H, Elorriaga I, Gebara
525 B, Gumse J, Heric A, Jensen E, Jones K, Knuts K, Maertens de Noordhout B, Martic A,
526 Normann B, Eijnde BO, Rasova K, Santoyo Medina C, Truyens V, Wens I, Feys P.
527 Responsiveness and clinically meaningful improvement, according to disability level of five
528 walking measures after rehabilitation in multiple sclerosis: a European multicenter study.
529 *Neurorehabil Neural Repair* 28: 621–631, 2014.
- 530 Benedetti MG, Piperno R, Simoncini L, Bonato P, Tonini A. Gait abnormalities in minimally
531 impaired multiple sclerosis patients. *J Mult Scler* 5: 363-368, 1999.
- 532 Bilodeau M, Keen DA, Sweeney PJ, Shields RW, Enoka RM. Strength training can improve
533 steadiness in persons with essential tremor. *Muscle Nerve* 23: 771-778, 2000.
- 534 Binder MD, Powers RK, Heckman CJ. Nonlinear input-output functions of motoneurons.
535 *Physiology* 35: 31-39, 2020.
- 536 Bohannon RW. Comfortable and maximum walking speed of adults aged 20-79 years: reference
537 values and determinants. *Age Ageing* 26: 15-19, 1997.
- 538 Broekmans T, Gijbels D, Eijnde BO, Alders G, Lamers I, Roelants M, Feys P. The relationship
539 between upper leg muscle strength and walking capacity in persons with multiple sclerosis. *Mult*
540 *Scler J* 19: 112-119, 2012.
- 541 Cabib C, Llufríu S, Casanova-Molla J, Saiz A, Valls-Sollé J. Defective sensorimotor integration
542 in preparation for reaction time tasks in patients with multiple sclerosis. *J Neurophysiol* 113:
543 1462-1469, 2015.

544 Carville SF, Perry MC, Rutherford OM, Smith ICH, Newham DJ. Steadiness of quadriceps
545 contractions in young and older adults with and without a history of falling. *Eur J Appl Physiol*
546 100: 527-533, 2007.

547 Castronovo AM, Mrachacz-Kersting N, Stevenson AJT, Holobar A, Enoka RM, Farina D.
548 Decrease in force steadiness with aging is associated with increased power of the common but
549 independent input to motor neurons. *J Neurophysiol* 120; 1616-1624, 2018.

550 Christou EA, Jakobi JM, Critchlow A, Fleshner M, Enoka RM. The 1- to 2-Hz oscillations in
551 muscle force are exacerbated by stress, especially in older adults. *J Appl Physiol* 97: 225-235,
552 2004.

553 Christou EA, Shinohara M, Enoka RM. Fluctuations in acceleration during voluntary
554 contractions lead to greater impairment of movement accuracy in old adults. *J Appl Physiol* 95:
555 373-384, 2003.

556 Clark DJ, Manini TM, Fielding RA, Patten C. Neuromuscular determinants of maximum
557 walking speed in well-functioning older adults. *Exp Gerontol* 48: 358-363, 2013.

558 Comber L, Galvin R, Coote S. Gait deficits in people with multiple sclerosis: a systematic review
559 and meta-analysis. *Gait Posture* 51: 25-35, 2017.

560 Davis LA, Allen SP, Hamilton LD, Grabowski AM, Enoka RM. Differences in postural sway
561 among healthy adults are associated with the ability to perform steady contractions with leg
562 muscles. *Exp Brain Res* 238: 487-497, 2020.

563 DeLuca GC, Alterman R, Martin JL Mittal A, Blundell S, Bird S, Beale H, Hong LS, Esiri MM.
564 Casting light on multiple sclerosis heterogeneity: the role of HLA-DRB-1 on spinal cord
565 pathology. *Brain* 136: 1025-1034, 2013.

566 Duchateau J, Enoka RM. Human motor unit recordings: origins and insight into the integrated
567 motor system. *Brain Res* 1409: 42-61, 2011.

568 Evangelou N, Esiri MM, Smith S, Palace J, Matthews PM. Quantitative pathological evidence
569 for axonal loss in normal appearing white matter in multiple sclerosis. *Annal Neurol* 47: 391-
570 395, 2000.

571 Farina D, Holobar A, Merletti R, Enoka RM. Decoding the neural drive to muscles from the
572 surface electromyogram. *Clin Neurophysiol* 121: 1616-1623, 2010.

573 Farina D, Negro F, Dideriksen JL. The effective neural drive to muscles is the common synaptic
574 input to motor neurons. *J Physiol* 592: 3427-3441, 2014.

575 Farina D, Negro F, Muceli S, Enoka RM. Principles of motor unit physiology evolve with
576 advances in technology. *Physiology* 31: 83-94, 2016.

577 Feeney DF, Mani D, Enoka RM. Variability in common synaptic input to motor neurons
578 modulates both force steadiness and pegboard time in young and older adults. *J Physiol* 596:
579 3793 – 3806, 2018.

580 Feeney DF, Meyer FG, Noone N, Enoka RM. A latent low-dimensional common input drives a
581 pool of motor neurons: a probabilistic latent state-space model. *J Neurophysiol* 118: 2238-2250,
582 2017.

583 Fling BW, Dutta GG, Horak FB. Functional connectivity underlying postural motor adaptation in
584 people with multiple sclerosis. *NeuroImage Clinical* 8: 281-289, 2015.

585 Fritzer NE, Keller J, Calabresi PA, Zackowski KM. Quantitative measures of walking and
586 strength provide insight into brain corticospinal tract pathology in multiple sclerosis.
587 *NeuroImage Clinical* 14: 490-498, 2017.

588 Fu L, Matthews PM, De Stefano N, Worsley KJ, Narayanan S, Francis GS, Antel JP, Wolfson C,
589 Arnold DL. Imaging axonal damage of normal-appearing white matter in multiple sclerosis.
590 *Brain* 121: 103-113, 1998.

591 Fuglevand AJ, Winter DA, Enoka RM. Models of recruitment and rate coding organization in
592 motor-unit pools. *J Neurophysiol* 70: 2470-2488, 1993.

593 Galea MP, Cofré LizM LE, Butzkueven H, Kilpatrick TJ. Gait and balance deterioration over a
594 12-month period in multiple sclerosis patients with EDSS ≤ 3.0 . *NeuroRehabilitation* 40: 277-
595 284, 2017.

596 Galganski ME, Fuglevand AJ, Enoka RM. Reduced control of motor output in a human hand
597 muscle of elderly subjects during submaximal contractions. *J Neurophysiol* 69: 2108-2115, 1993.

598 Goldman MD, Motl RW, Sagnelli J, Pula JH, Sosnoff JJ, Cadavid D. Clinically meaningful
599 performance benchmarks in MS: timed 25-foot walk and the real world. *Neurology* 81: 1856-
600 1863, 2013.

601 Gould JR, Reineberg AE, Cleland BT, Knoblauch KE, Clinton GK, Banich MT, Corboy JR,
602 Enoka RM. Adjustments in torque steadiness during fatiguing contractions are inversely
603 correlated with IQ in persons with multiple sclerosis. *Front Physiol* 9: 1404, 2018.

604 Gunte I, Hunter GR, McCurry BD, Bolding MS, Roy JL, McCarthy JP. Age and gender
605 differences in hip extension and flexion torque steadiness. *Gerontology* 56: 533-541, 2010

606 Gutierrez GM, Chow JW, Tillman MD, McCoy SC, Castellano V, White LJ. Resistance training
607 improves gait kinematics in persons with multiple sclerosis. *Arch Phys Med Rehabil* 86: 1824-
608 1829, 2005.

609 Hadjimichael O, Vollmer TJ, Oleen-Burkey M. Fatigue characteristics in multiple sclerosis: the
610 North American Research Committee on Multiple Sclerosis (NARCOMS) survey. *Health Qual*
611 *Life Outcomes* 6: 100, 2008.

612 Hamilton LD, Thomas E, Almklass AM, Enoka RM. A framework for identifying adaptations
613 responsible for differences in pegboard times between middle-aged and older adults. *Exp*
614 *Gerontol* 97: 9-16, 2017.

615 Holobar A, Zazula D. Multichannel blind source separation using convolution kernel
616 compensation. *IEEE Tran Signal Process* 55: 4487-4496, 2007.

617 Holmes MR, Gould JR, Peña-González I, Enoka RM. Force steadiness during a co-contraction
618 task can be improved with practice, but only by young adults and not by middle-aged or old
619 adults. *Exp Physiol* 100: 182-192, 2015.

620 Justice JN, Mani D, Pierpoint LA, Enoka RM. Fatigability of the dorsiflexors and associations
621 among multiple domains of motor function in young and old adults. *Exp Gerontol* 55: 92-101,
622 2014.

623 Kearney J, Schneider T, Yiannakas MC, Altmann DR, Wheeler-Kingshott CA, Ciccarelli O,
624 Miller DH. Spinal cord grey matter abnormalities are associated with secondary progression and
625 physical disability in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 86: 608-614, 2015.

626 Kieseier BC, Pozzilli C. Assessing walking disability in multiple sclerosis. *Mult Scler* 18: 914-
627 924, 2012.

628 Kluger BM, Krupp LB, Enoka RM. Fatigue and fatigability in neurologic illnesses: proposal for
629 a unified taxonomy. *Neurology* 80: 409-416, 2013.

630 Laidlaw DH, Bilodeau M, Enoka RM. Steadiness is reduced and motor unit discharge is more
631 variable in old adults. *Muscle Nerve* 23: 600-612, 2000.

632 Laine CM, Martinez-Valdes E, Falla D, Mayer F, Farina D. Motor neuron pools of synergistic
633 thigh muscle share most of their synaptic input. *J Neurosci* 35: 12207-12216, 2015.

634 Liddell EGT, Sherrington C. Recruitment and some other factors of reflex inhibition. *Proc*
635 *Royal Soc London B* 97: 488-518, 1925.

636 Loy BD, Taylor RL, Fling BW, Horak FB. Relationship between perceived fatigue and
637 performance fatigability in people with multiple sclerosis: a systematic review and meta-
638 analysis. *J Psychosomatic Res* 100: 1-7, 2017.

639 Macke JH, Buesing L, Cunningham JP, Byron MY, Shenoy KV, Sahani M. Empirical models of
640 spiking in neural populations. *NIPS* 24: 1350-1358, 2011.

641 Mani D, Almklass AM, Hamilton LD, Vieira TM, Botter A, Enoka RM. Motor unit activity,
642 force steadiness, and perceived fatigability are correlated with mobility in older adults. *J*
643 *Neurophysiol* 120: 1988-1997, 2018.

644 Marmon AR, Pascoe MA, Schwartz RS, Enoka RM. Associations among strength, steadiness,
645 and hand function across the adult life span. *Med Sci Sports Exerc* 43: 560-567, 2011.

646 Motl RW, Sandroff BM, Suh Y, Sosnoff JJ. Energy cost of walking and its association with gait
647 parameters, daily activity, and fatigue in persons with mild multiple sclerosis. *Neurorehabil*
648 *Neural Repair* 26: 1015-1021, 2012.

- 649 Negro F, Holobar A, Farina D. Fluctuations in isometric muscle force can be described by one
650 linear projection of low-frequency components of motor unit discharges. *J Physiol* 587: 5925-
651 5938, 2009.
- 652 Newsome SD, Wang JI, Kang JY, Calabresi PA, Zackowski KM. Quantitative measure detect
653 sensory and motor impairments in multiple sclerosis. *J Neurol Sci* 305: 103-111, 2011.
- 654 Ng AV, Miller RG, Gelinias D, Kent-Braun JA. Functional relationships of central and peripheral
655 muscle alterations in multiple sclerosis. *Muscle Nerve* 29: 843-852, 2004.
- 656 Pereira HM, Spears VC, Schindler-Delap B, Yoon T, Nielson KA, Hunter SK. Age and sex
657 differences in steadiness of elbow flexor muscles with imposed cognitive demand. *Eur J Appl*
658 *Physiol* 115: 1367-1379, 2015.
- 659 Petrova PN, Carassiti D, Altmann DR, Baker D, Schmierer K. Axonal loss in the multiple
660 sclerosis spinal cord revisited. *Brain Pathol* 28: 334-348, 2018.
- 661 Rice DA, McNair PJ, Lewis GN, Mannion J. Experimental knee pain impairs submaximal force
662 steadiness in isometric, eccentric, and concentric muscle actions. *Arthritis Res Ther* 17: 259,
663 2015.
- 664 Rice CL, Vollmer TL, Bigland-Ritchie B. Neuromuscular responses of patients with multiple
665 sclerosis. *Muscle Nerve* 15: 1123-1132, 1992.
- 666 Schlaeger R, Papinutto N, Zhu AH, Lobach IV, Bevan CJ, Bucci M, Castellano A, Gelfand JM,
667 Graves JS, Green AJ, Jordon KM, Keshavan A, Panara V, Stern WA, von Büdingen HC,
668 Waubant E, Goodin DS, Cree BA, Hauser SL, Henry RG. Association between thoracic spinal
669 gray matter atrophy and disability in multiple sclerosis. *JAMA Neurol* 72: 897-904, 2015.
- 670 Sebastião E, Bikkaert RE, Hubbard EA, Motl RW. Gait variability and energy cost of
671 overground walking in persons with multiple sclerosis: a cross-sectional study. *Am J Phys Med*
672 *Rehabil* 97: 646-650, 2018.
- 673 Sosnoff JJ, Sandroff BM, Motl RW. Quantifying gait characteristics in persons with multiple
674 sclerosis with minimal disability. *Gait Posture* 36: 154-156, 2012.
- 675 Thompson CK, Negro F, Johnson MD, Holmes MR, Miller Mcpherson L, Powers RK, Farina D,
676 Heckman CJ. Robust and accurate decoding of motoneuron behavior and prediction of the
677 resulting force output. *J Physiol* 596: 2643-2659, 2018.
- 678 Tracy BL, Enoka RM. Older adults are less steady during submaximal isometric contractions
679 with the knee extensor muscles. *J Appl Physiol* 92: 1004-1012, 2002.
- 680 Tracy BL, Mehoudar PD, Ortega JD. The amplitude of force variability is correlated in knee
681 extensor and elbow flexor muscles. *Exp Brain Res* 176: 448-464, 2007.

682 Vogt J, Paul F, Aktas O, Müller-Wielsch K, Dörr J, Dörr S, Bharathi S, Glumm R, Schmitz C,
683 Steinbusch H, Raine CS, Tsokos M, Nitsch R, Zipp F. Lower motor neuron loss in multiple
684 sclerosis and experimental autoimmune encephalomyelitis. *Ann Neurol* 66: 310-322, 2009.

685 Zijdewind I, Prak RF, Wolkorte R. Fatigue and fatigability in persons with multiple sclerosis.
686 *Exerc Sport Sci Rev* 44: 123-128, 2016.

687

688 **Figure Legends**

689 **Figure 1.** A. The experimental setup for measuring muscle strength and force steadiness for the
690 dorsiflexors (Above) and the plantar flexors (Below) of the right leg. High-density grid electrodes were
691 placed over the tibialis anterior, medial gastrocnemius, and soleus muscles. B. Participant's maintained a
692 steady contraction for 30 s at 10% and 20% MVC force. C. Monopolar signals were recorded during
693 submaximal, isometric contractions. The high-density grid recordings resulted in bipolar
694 electromyographic recordings that were subsequently decomposed into motor unit discharge times. D.
695 The discharge times of 9 motor units during a steady, isometric contraction.

696 **Figure 2.** Regression models for fast-walking speed (A, B) and walking endurance (C, D) for the
697 participants in the MS (n = 18; A, C) and control (n = 18; B, D) groups. The explanatory variables for
698 each model were as follows: A, force steadiness of the plantar flexors at 20% MVC force and
699 force steadiness for the dorsiflexors at 10% MVC; B, force steadiness of the dorsiflexors at 20%
700 MVC force and the filtered Q values for the plantar flexors; C, force steadiness of the plantar
701 flexors at 20% MVC force and force steadiness for the dorsiflexors at 10% MVC; D, MVC
702 torque for the plantar flexors of the non-dominant leg and MVC torque for the dorsiflexors of the
703 dominant leg.

704

705

706